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THE PRACTICING PHYSICIAN IN THE FIELD OF PREVENTIVE MEDICINE*

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AS YOU have been told, I am a teacher of medical students. Now it is the function of the teacher to prepare these men for their future work. One must be very careful not to prepare the student for the type of medical practice of a past generation or for the practice of medicine as it presents itself at the present time. For these young men are to be the physicians of the next generation, and must be prepared to meet that responsibility.

It is necessary, therefore, for their instructors to think, even to live, in the future, and to attempt to predict what the social structure will be during the next thirty to fifty years, and to try to understand what problems in medical care will arise. It is necessary to predict the probable prevalence of the various types of illness and on the basis of this prediction to plan for suitable provision for prevention of these illnesses and to prepare for the suitable care of the sick. The future development of hospitals, of nursing homes, of plans for domiciliary and for ambulatory medical care must be made. The utilization to greatest advantage of physicians, nurses and other professional personnel must be interrelated in the broad over-all plan. The role of the local community, the state and the federal Government in the provision for comprehensive medical service for all the people must be predicted. Furthermore, the role of the voluntary health agencies, and the important part that they will play in prevention of illness and in medical care during the coming generation, must be understood.

At the outset it must be quite clear that my major thesis is that medicine is a social science. This is somewhat of a departure from the concepts of the past two generations. The whole tendency in medicine since the time of Pasteur has been to concentrate upon a study of disease: its cause, its pathology and its specific treatment. In this avid search for a better understanding of disease, it was forgotten that it was an individual who was sick, and that the primary concern was with a person, rather than with a disease in him. The great physicians of all time have understood that medicine is not a study of disease, but a study of man: an individual who is a member of a family and who is part of a community. I believe with them that the purpose of medicine is to study the various factors that affect the health status of the members of the group, and to provide such measures of a sanitary, medical or social nature as are necessary to promote the health of the individual, the family and the community. In essence, then, the purpose of medicine is to make available to all the people, in the greatest possible degree, the achievements of science as they relate to the promotion of health and to the prevention and treatment of disease.

With this concept of medicine, the future of this science and art are considered. As noted above, the planning for comprehensive medical care of the future requires a gift of prophecy. But prophecy is not so difficult as it may seem at first glance. It would not be possible, of course, to draw in all the details of the picture, but the broad outlines are quite clear. They may be determined in advance by one of two commonly used procedures:

By the use of trend lines. By this method the natural history of disease for past generations is determined, and a definite trend line is established and is then extended to the future. Past experience has shown that the resulting conclusions closely approximate actual conditions as they develop.

Another method is to study successful procedures that have already been developed in an area that is perhaps more advanced in its social achievements than one's own. One may make the assumption that a successful measure, once it is clearly demonstrated, will ultimately be applied wherever a similar situation may be encountered. A simple example in the national economy is the plan of the Tennessee Valley Authority. This procedure has been so successful in the conservation of national resources that the method undoubtedly will be applied in the future to other great river valleys.

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There are certain clearly defined trend lines that make it possible to draw some broad conclusions about the incidence and prevalence of disease during the coming generation. The following events may be predicted:

There will be a decline in deaths from the major acute infections of all types. This will include tuberculosis. Not only will the death rate from these diseases decline, but the prevalence of each of these diseases in the community will diminish greatly.

There will be a decline in infant and in childhood morbidity and mortality.

Because of the increased urbanization of the population, there will be a marked increase in health problems relating to industry. There will be an increase in accidents and other hazards of communal living.

An increase will occur in mental disease, but this increase will be selective, with a diminution of certain types of mental disease, and a marked increase of senility and other mental disturbances occurring in the aged.

Most important of all will be the great increase in the degenerative diseases of all types. Especially important are heart disease, neoplastic disease, arthritis, diabetes and the like. This increase in the degenerative diseases will be, for the most part, due to the change in the composition of the population, and will result in a marked change in the community program for medical care, and for prevention of illness and promotion of public health.

These changes in the natural history of disease will result in a demand for quite a different type of medical care. There will be an overwhelming demand for provision, by the community, of a comprehensive plan of medical service, which will be *all-inclusive* and which may be paid for on a voluntary basis, or possibly on a compulsory basis. (The first step in this plan has already been taken with the rapid development of the Blue Cross Plan, which provides prepayment for hospitalization.) The development of a plan for comprehensive medical care on a prepaid basis is the very obvious and logical next step.

The increase in the older age groups will result in the development of suitable facilities for care of prolonged chronic illness, including mental degeneration. Adequate old-age pensions are an obvious and necessary part of this social program.

A comprehensive all-inclusive plan for medical care on a prepayment basis inevitably initiates strong emphasis on preventive services. It has already been shown, in the few experiments that have been tried, that an active, aggressive preventive service is generally effective in diminishing the costs of the subsequent treatment of serious acute disease, and is particularly effective in the prevention of chronic illness.

Thus, the person who makes the prepayment for comprehensive medical care for himself and his family is in reality assuming responsibility both for preventive medicine and for curative service.

Community Responsibility in Comprehensive Medical Care

The community itself will assume responsibility for the prevention of all illness that is due directly to the hazards of community life. For example, the community will, as at present, attempt to prevent communicable disease. It will promote the health of the worker, and will actively combat causes of injury and death due to accidents or violence. Promotion of a suitable environment to aid in prevention of illness of the people is an established community function and obviously will continue to be. The education of all the people in the principles of hygiene and preventive medicine on a comprehensive basis will be greatly developed as a community function.

In addition, it seems probable that the organization for health protection and for actual medical services will be combined as a single unit, and that this service will be administered by the local community. For it is becoming more and more clear that the prevention of illness and the promotion of health cannot be separated from the diagnosis and treatment of disease. It is clear that in the future those services will be provided for, and will be administered as a single unit.

Furthermore, it now seems obvious that the mass methods for prevention of illness that have been so successful in the past will not continue to be equally successful during the coming years. The reason is that mass procedures in prevention cannot be applied with a high degree of effectiveness to the control of degenerative disease. It is true that these methods can be modified somewhat and may be used to supplement and to strengthen the basic unit plan for comprehensive medical care. But the keystone of any plan for providing comprehensive medical care for the community is the physician who is in medical practice. As I have indicated above, the practice of medicine will not be the type of practice of the past generation, nor as it is carried out at the present time. For, in a unit plan for medical care, the physician must devote his major efforts to the prevention of illness rather than to treatment. The reason for this is that only through the development of preventive measures on an individual basis can the ravages of these chronic diseases be ameliorated. This is true of such conditions as heart disease, cancer, arthritis and the other degenerative diseases of adult life. It is particularly true of tuberculosis.

The Practitioner of Medicine and Pulmonary Tuberculosis

The more pertinent part of the discussion relates to the special interests of this organization. What will be the plan for the control of pulmonary tuberculosis in the future? It seems clear that the major responsibility for prevention and control of tuberculosis will rest upon the practicing physician.

How can this be true? More and more in recent years the control of tuberculosis has been taken out of the hands of the practicing physician. Extensive x-ray surveys of large populations, the follow-up examination of contacts by health-department personnel, the immediate hospitalization of all patients with active cases of tuberculosis — all these are mass methods of control that have been carried out under community auspices.

But it must be remembered that the control of a disease is determined by its epidemiology. The epidemiologic trend in tuberculosis can be assessed as follows:

The disease will undoubtedly continue to decline both in mortality and in morbidity.

Tuberculosis in infancy will gradually disappear. The disease has never been of great importance in children of school age.

The age at which primary infection will occur will be postponed. Within a few years, 90 per cent of young people of college age will have a negative tuberculin reaction.

Tuberculosis will not be an important cause of death in the younger and middle decades of life. Deaths from the disease will occur, for the most part, in the older age groups — that is, the sixth and seventh decades.

There will be no relative increase in the Negro population. The ratio of colored to whites will remain about 10 per cent, but there will be a much wider dispersal of colored people to the industrial centers. Since the death rate from tuberculosis in Negroes in industrial centers is three or four times that of whites, it becomes obvious that concentrated effort will be placed on control of the disease in these people.

Tuberculosis will rapidly become a true *social disease* — that is, a disease that accompanies poverty, ignorance, negligence and carelessness. People living under good social and economic conditions will almost never die of the disease.

It is not probable that economic depressions or social upheavals will produce a marked increase in tuberculosis. It is true that tuberculosis did increase in certain areas in the world during the war years, where hunger, displacement and very unhygienic conditions prevailed. This increase did not occur within the boundaries of the United States. The nation passed through a great financial depression (1929–1938) followed by a disastrous war, with no resultant increase in deaths from tuberculosis. The reasons probably were that there was no true hunger, no severe hardship and no injurious lowering of living standards during these years.

These observations compel one to conclude that the increase in facilities for distribution of necessary food, the more widely spread knowledge of the principles of healthful living, better understanding of good housing and the leveling off of income, with few rich and few poor, have been, and will continue to be, important factors in the prevention of incidence of and death from tuberculosis. Unless a world-wide catastrophe interferes, it seems clear that social factors will continue to favor reduction rather than increase of tuberculosis.

As the disease declines in incidence, there will be less and less need for specific immunization procedures,* which are mass procedures. There will be more and more need for specific therapy. At this point it is encouraging to note that the discovery of effective specific therapy in tuberculosis is much nearer than it was deemed possible twenty or even ten years ago.

One important epidemiologic principle in tuberculosis is that the disease, if diagnosed during its early stages, can be handled effectively. Thus, it is necessary to develop better technics for early detection of tuberculosis. Perhaps it is more important still to develop a more effective social machinery, so that this diagnostic service can be made readily available to all susceptible persons, and particularly for those who are at greatest risk.

Application of Control Measures

Many mistakes, most of them quite justifiable, have been made in the application of mass procedures for early diagnosis of tuberculosis. Dr. Chadwick, formerly state health officer of Massachusetts, who instituted mass x-ray surveys nearly twenty years ago for children of school age, demonstrated that this procedure was a waste of time. The mass x-ray methods that are now so popular, with mobile units offering free x-ray examinations of the chest to various groups of society, are undoubtedly of real educational value, but in many surveys, the actual number of cases of tuberculosis that are found is disappointingly small. Dr. Herbert Edwards has arranged certain social groups, in order of diminishing importance, in which the mass x-ray technic is of real benefit:

*At the present time, B.C.G. may be utilized effectively as a specific immunization procedure, in selected cases.

For example, young adults who have a negative tuberculin reaction and who have intimate and frequent contact with cases of open pulmonary tuberculosis should receive the protection of B.C.G. In this category belong medical students, interns, nurses, hospital attendants and others who are closely associated with the care of the sick.

Older age groups of people living under substandard conditions, particularly unemployed elderly men who are on the relief and welfare rolls.

Negro populations living under congested, substandard conditions, particularly in the large industrial centers. One does not expect to find more tuberculosis in these groups than would be found in white populations living in similar conditions, but the cases that are found are much more important, because the mortality rate is so high in these infected persons.

Industrial workers subjected to toxic dusts, particularly silica dust.

Groups subjected to continuous exposure to the disease, such as young physicians, nurses and attendants who work with cases of open tuberculosis.

The mass x-ray method may also be employed to advantage on patients as they are admitted to a general hospital, and some authorities believe it worth while to take an x-ray film on young adults who are seen for the first time in the clinic or in private practice. There is also some practical advantage in giving a pre-employment x-ray examination to industrial workers, and also to applicants for civil service positions, particularly to school teachers and others who work with children. Beyond this point mass x-ray examinations of the chest do not yield positive results that are commensurate with the cost.

How Shall Control Measures Be Applied?

On the basis of the epidemiologic trends that have just been noted, one sees readily that tuberculosis, the great destroyer of mankind of a century ago, has been dethroned, and that the disease will, within a relatively short time, play a minor part in the total picture of human illness and misery. It will then be placed in the category that its importance warrants. Prevention and control of tuberculosis will not be organized by the community as a program that is separate from the general community plan for comprehensive medical care; rather, tuberculosis control will soon become an essential and integral part of the community-wide plan for adequate medical service. This simply means that tuberculosis in the relatively near future will not be attacked as a *disease*, as in the past. The concept will be that people should be provided with adequate, comprehensive medical care, including preventive service, early and accurate diagnosis, effective, co-ordinated treatment and, in necessary cases, with proper rehabilitation. This policy will be followed for all chronic diseases of middle and past middle life. It is in this category that tuberculosis will fall.

The tuberculosis associations have been the most effective organizations in America in bringing about the remarkable results that have been achieved in control. As is true of all voluntary health organizations, the purpose of the tuberculosis association has been, from the outset, to eliminate the conditions that made its existence necessary, and thus eventually to eliminate itself. This happy state of development has not yet arrived. Much remains to be done, but the objectives are clearly marked and the goal is not too far away. It seems quite clear, as I said at the outset, that the prevention and control of tuberculosis will become in great part, and within a relatively few years, the province of the practitioner of medicine. Within the next generation, the control activities in tuberculosis will not be a special field of endeavor but will be, I firmly believe, incorporated as an integral part of the comprehensive community-wide plan for preventive and curative services.

THE EFFECT OF NASAL AND SINUS SURGERY UPON THE MANIFESTATIONS OF ALLERGY*

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THE effect of nasal and sinus surgery upon the manifestations of allergy has long been controversial. The purpose of this paper is to present a point of view based upon about twenty years of rhinologic research in the Allergy Clinic of the Massachusetts General Hospital, and upon experience in dealing with a considerable number of patients as a surgeon in the Massachusetts Eye and Ear Infirmary and in private practice. It is easy to report statistical studies in an effort to support an opinion, but scientific truth is rarely reached by such a method. On the contrary, one must observe what happens without bias or preconceived ideas and then allow the resulting experience to form the basis for one's conclusions and for the advice given to the individual patient.

An effort has been made to present "unbiased" statistics in previous publications.[1-7] These papers include studies of 1059 patients, over three fourths of whom had manifestations of allergy and over half of whom had asthma. Because of the technical difficulties of sinus surgery, reference is made to a study[7] of 276 cases of frontal sinus dealing with the special problems of this sinus. A further investigation is now being made at the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary of 272 cases of vasomotor rhinitis (in which 51 patients had asthma), and 255 patients with asthma (including the 51 just mentioned) who have undergone nasal and sinus surgery. Over 100 of these cases have been previously reported,[3] but about 400 have not.

A special research worker is now engaged in obtaining as much information as possible from the last two groups. The information obtained will be published at a later date, but a few of the preliminary results are mentioned below.

The surgical questions to which everyone desires an answer are the following:

What is the effect of nasal and sinus surgery upon the nose? Upon the asthma?

Is it possible to select in advance the patients with asthma or vasomotor rhinitis patients who will receive benefit from such surgery?

How complete should the nasal and sinus surgery be in the asthmatic patient — and in the vasomotor-rhinitis patient?

Can nasal polyps and polypoid degeneration in these patients be explained adequately?

Each of these four questions is considered separately in the four sections that form the body of this paper. To limit the discussion, reference is made only to asthma, vasomotor rhinitis and nasal and sinus polyposis.

EFFECT OF NASAL AND SINUS SURGERY

At the Massachusetts Eye and Ear Infirmary and the Massachusetts General Hospital, sinus surgery has resulted in permanent cure in 10 per cent of the asthmatic patients and in improvement for two years or more in about 50 per cent; the remaining cases have been failures immediately or after a few weeks or months of improvement.

Rackemann[8] is of the opinion that, even though there may be a limited period of improvement in the asthma following sinus surgery, the long-term trend is toward worsening. I believe that this opinion is held by Dr. Rackemann because of the many patients with severe asthma referred to him from all parts of the world, many of whom have had previous operations on the sinuses. The specific problem of determining whether any single case of the 255 cases of asthma now being studied became worse as a direct result of sinus surgery is now under careful investigation. There is no question that poorly conceived and very drastic sinus surgery can result in the worsening of the *nasal* status, but this can be avoided by considerations of practical surgical technic. In general, the results *in the nose* have been satisfactory in approximately 75 per cent of cases, provided the patient is followed for prevention of recurrent polyposis by destruction of such tissue in its incipient stages. Diathermy coagulation or simple excision will accomplish this purpose.

In vasomotor rhinitis my own personal results have been about 80 per cent relief of nasal obstruction, with somewhat less success in the control of rhinorrhea and sneezing. More exactly, 74 per cent of 234 surgical results were satisfactory (Tables 1, 2 and 3).

Interpretation of results is not easy. In asthma especially, the patient may report a widely different result in his condition depending upon the adventitious presence of a head cold or upon the length of time that he is followed. For example, one patient, two years after nasal surgery, reported that his asthma was 95 per cent better and expressed great appreciation for the result in the nose and

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in the chest. Recently, he appeared with a head cold; he had started some wheezing; he then said that his asthma improvement was only slightly over the preoperative level, although his nose bothered him only moderately. The same patient had made a similar reversal under the same circumstances about a year earlier. There was no question about his improvement; it was merely that his mood was one of elation when he was at his best and the contrary when he was troubled by an acute upper respiratory infection.

A second patient reported that she was better for a month after the operation, when the asthma became just as severe as ever. It remained so during the succeeding nine months and then suddenly cleared up after the death of her mother. Whereas the patient had been bed ridden for weeks at a time, she was able to do whatever she wished when she was interviewed, and had had only slight wheezing but not for more than ten minutes at a time; she had had no particular discomfort from it during the preceding six months. Prior to the nasal operation, her asthma had been classified as intrinsic, after exhaustive studies.

These cases suggest a possible explanation for some of the discrepancies in the widely varying reports regarding the effect of nasal and sinus surgery upon asthma.

Table 1. *Surgical Results in 234 Cases of Vasomotor Rhinitis.*

Results	No. of Cases	Percentage
Poor	6	2.6
Fair	54	23.1
Good	112	47.8
Excellent	54	23.1
Cure	8	3.4

Table 2. *Follow-up Period in 234 Cases of Vasomotor Rhinitis.*

Follow-up Period	No. of Cases	Percentage
yr.		
Under 1	53	22.6
1–2	80	34.2
3–5	64	27.4
6–10 or more	37	15.8

Table 3. *Results in 181 Cases of Vasomotor Rhinitis Followed for One to Ten Years or More.*

Results	No. of Cases	Percentage
Poor	6	3.3
Fair	41	22.7
Good	91	50.3
Excellent	37	20.4
Cure	6	3.3

Can the Asthmatic or Vasomotor-Rhinitis Patients who will Receive Benefit from Operation be Selected in Advance?

With present knowledge, the answer to this question must, unfortunately, be no. However, from the surgical results referred to above, it is possible to predict the probability of a good result in a high percentage of vasomotor-rhinitis cases and in a moderate number of patients who have either intrinsic asthma with nasal involvement or infected extrinsic asthma in which the extrinsic factors have received adequate management.

It is universally recognized that a nasal surgical procedure, varying from the simple removal of a polyp to extensive and formidable undertakings, occasionally "cures" intrinsic or reflex asthma. The same statement holds true for infected extrinsic asthma, provided that the extrinsic factors are skillfully managed. The argument is not whether this can happen, but in what percentage of cases improvement or cure will take place.

Although this favorable change may supervene even in patients with status asthmaticus, it is obvious that when operation is resorted to only with the most severe cases it is likely to be disappointing because the course of the disease is downward anyway. Thus, sinus surgery is brought into disrepute by the assumption that it not only failed to interrupt the downward cycle but actually precipitated it. I have seen nasal operations that made the nose worse, but never the asthma. This is not to say that there have been no cases in which the asthma became worse; it is rather to submit the opinion that the asthma would have become worse whether the surgery had been done or not.

Because of the privilege of working in close collaboration with highly skilled allergists, it has been my policy that the allergist should review each patient carefully and treat him for extrinsic factors when these are demonstrable or probable. The intrinsic cases have usually been under the management of the allergist so long as improvement occurred. Therefore, the great majority of cases operated on consisted of the so-called "failures" by the allergist — that is, the allergist had reached the conclusion that his therapy had failed to help the patient adequately, or the patient had so decided for himself. In such cases it seems reasonable not to postpone operation year in and year out if there is a possibility of benefit to the patient. However, because there may be no improvement in the asthma after nasal surgery, it is desirable for the patient to have enough wrong with the nose and to have enough nasal complaints to feel that his *nose* is made better, not worse, by the operation. Local improvement in the nasal disease can be obtained in 80 per cent of the cases from the patient's

point of view and in about 70 per cent from the rhinologist's point of view, provided there is an adequate follow-up period.

On the other hand, if the patient has few or no nasal complaints and merely an x-ray report of extensive sinus disease, he may complain bitterly that the nose is worse, especially if any radical procedure is attempted upon the frontal sinuses.

It is the patient who is treated, not the x-ray report of his sinus. This statement may seem trite, but there are specialists in rhinology who occasionally undertake extensive and very radical sinus operations based upon x-ray findings alone in patients who have relatively mild nasal complaints or associated manifestations of allergy.

In young people, mild infected extrinsic asthma often disappears after surgical procedures designed to induce nasal breathing in vasomotor rhinitis cases or to accomplish the same purpose and deal conservatively with polypoid sinusitis.

In vasomotor rhinitis, operation is advised on the basis of both local pathologic findings *and* symptomatic complaints. Since, in the first 84 of the operative group now numbering 272 cases, satisfactory alleviation of symptoms (especially of nasal obstruction) occurred in about 80 per cent of the cases, it was considered reasonable to advise operation in 272 of a group of 1018 patients. In the selection of these cases, about 18 per cent of whom had asthma, the first purpose of operation was to provide the patient with nasal cavities improved mechanically and physiologically.

Since asthma develops sooner or later in about 15 per cent of patients with vasomotor rhinitis, there is always the risk of asthma after any form of nasal operation in these patients. In 1 case a nasal fracture occurred, and asthma supervened; when the deviated septum was corrected and the nasal mucosa stabilized, the asthma disappeared. This appears to have been a simple reflex asthma. In a case presented below, the excision of nasal polyps was followed in three days by the onset of intrinsic asthma, which has continued over an eleven-year period and is likely to go on indefinitely. In another patient, a middle-aged adult who had nasal and sinus polyposis with vasomotor rhinitis, nasal operation relieved all nasal complaints but was followed by the onset of asthma. Allergists consider the possibility of development of asthma in some patients with vasomotor rhinitis an argument for attempting to control the symptoms of the nasal disease.

In 500 cases of asthma previously reported[3] about 45 per cent of patients had vasomotor rhinitis, but only about 15 per cent of vasomotor-rhinitis patients had asthma. Once the asthma has developed, the presence of vasomotor rhinitis should not be a contraindication to any nasal operation.

Extent of Nasal and Sinus Surgery in Patients with Asthma and Vasomotor Rhinitis

In 1936 Cooke and Grove[9] reported 120 cases of sinus surgery in asthma and separated the group into patients who had had a "complete operation" and those with an "incomplete operation." They were able to show that 86 per cent of the patients more thoroughly operated on had improvement in the asthma in contrast to 39 per cent of those who had incomplete procedures.

These authors omit specific details of surgical technic, but the reader has the impression that the operation of choice was the Caldwell–Luc antrum, intranasal ethmoidectomy, and sphenoidectomy. The only frontal-sinus procedure was "enlargement of the nasofrontal duct" in 6 cases — meaning, presumably, that the nasofrontal duct or the ethmoidal drainage pathway of the frontal sinus was excised up to the ostium. This point is not specifically mentioned but may be assumed because such a measure frequently helps frontal-sinus disease, whereas enlargement of the frontal ostium intranasally is widely repudiated by rhinologists because of the tendency of the operative opening to close.

The surgical procedure outlined above is ordinarily the best in patients with asthma, but submucous resection of the septum is also useful, for the following reasons: it corrects mechanical obstruction; fibrosis between the flaps in vasomotor rhinitis helps to lessen bogginess of the septal mucosa — a large area of the nasal lining; the intranasal approach to the ethmoids is made easier; nonobstructive septums, when the nasal mucosa is thin, may become obstructive to nasal breathing and to sinus ostial drainage points when the membrane becomes turgescent.

Intranasal ethmoidectomy is an easier technical procedure after submucous resection of the septum and becomes a much faster and safer one — that is, the time required to correct the septum is usually more than saved in the shortening of the period required for the other parts of the operation. It also ensures that the septum will not be a factor mechanically in obstructing sinus ostia. Of course, if polyps are present, they are removed during the nasal or sinus procedure.

If vasomotor rhinitis is present, subepithelial diathermy coagulation cauterization is carried out to each inferior turbinate, as follows:

A slender unbreakable needle is introduced into the nonciliated anterior end of the inferior turbinate and passed subepithelially to but not through the posterior tip. An indifferent electrode is in place on the patient's shoulder held by a nurse. Intratracheal ether anesthesia is discontinued, and inflammable anesthetics are removed from the operating room. The room is aired out to dispel any inflammable concentration of ether vapor near

the floor. The usual post-nasal pack is left in situ, as is the uterine tape packing, wet with saline solution, in the oropharynx and hypopharynx. A Davis–Bovie machine, set on "coagulation" at 25, is attached to the needle, and cauterization is applied for about ten seconds as the needle is slowly withdrawn. Three streaks are usually necessary for each inferior turbinate; these streaks radiate like a fan from the same puncture wound. No other tissue than the inferior turbinate is so treated. The coagulated tissue, when organized, shrinks sufficiently to allow all sympathomimetic drugs to be discarded, even in the presence of acute rhinitis. The hyperplastic mucosa regresses toward normal, turgescence is lessened, and hyperesthesia is moderately diminished, but adequate function is retained, with an undamaged ciliary mechanism.

In vasomotor-rhinitis patients without asthma, correction of deviations of the septum is carried out, nasal polyps are removed, and any necessary sinus procedure is limited to that which can be done intranasally to the ethmoids, antrums and sphenoids (chiefly the ethmoids). Nasal obstruction will not be lessened in the majority of cases unless the diathermy technic just described is carried out — that is, in cases of vasomotor rhinitis much attention should be given to the nasal cavities, with less attention to the sinuses. Further sinus work can always be done at a later date if necessary. *In general, sinus surgery in vasomotor-rhinitis patients will not relieve nasal obstruction.*

The first statement made in this paper was that the subject is controversial. This particularly applies to the term "complete operation." What has been outlined above, or what Grove means by a complete operation, may seem very incomplete to other rhinologists. The following case is evidence of this fact:

In 1937 a 57-year-old woman complained of asthma 3 days after nasal polyps had been excised in the Out Patient Department of the Massachusetts General Hospital. She was studied and treated for intrinsic ("reflex") asthma but was not helped. A Caldwell–Luc antrum operation was done on one side 8 months later and on the other side 10 months later. These procedures had no effect upon the asthma. The patient became discouraged and went to a private clinic in Boston, where a rhinologist and his associates in allergy believed that sinus disease had caused the asthma. It was decided to empty all sinuses. In 1940 this was done. The antrums were operated on again by the Caldwell–Luc technic. A Lynch-type, frontal-ethmoid-sphenoid operation was carried out on one side and, 2 weeks later, on the other side.

For the next 6 months the asthma was greatly improved but after that short interval it became the same as before. However, certain sequelae from the operation developed: the patient had double vision; between 1940 and 1948 she had nine orbital abscesses on one or both sides, with intervals of about 1 year between attacks. Very severe headaches developed. In 1948 pyoceles were found in the frontal sinuses. She remained in bed for about 3 years after the operation and lost 46 pounds in weight. She returned to the Allergy Clinic of the Massachusetts General Hospital for treatment in 1946, where she regained most of the weight she had lost and the asthma became better but was still intractable. One flare-up of orbital swelling was so severe as to suggest cavernous-sinus thrombophlebitis. It was not necessary to resort to external incision and drainage until January, 1948, when she was admitted to the Massachusetts Eye and Ear Infirmary and a surgeon operated on the left frontal sinus by the Lynch technic, suturing tantalum foil to the orbital periosteum in an attempt to induce nasal drainage from the frontal sinus.

She still had infected frontoethmoidal cells at that time, and a part of the floor of the frontal sinus was present. Excision was done. In spite of this operation left-sided orbital swelling continued to develop, resulting in a frontal fistula. This drained pus intermittently. Finally, the tantalum foil was removed, after which the frontal fistula closed satisfactorily.

Later, when the patient visited the clinic in December, the note in the record stated, "Unimproved but no worse as regards the asthma." At that time the patient said that her "sinuses were acting up again."

Here is a case in which a "complete operation" was done, in that an attempt was made to remove polypoid tissue from all sinuses. The local condition of the nose was certainly made worse by this procedure, and the asthma was not improved, except for a period of 6 months. The double vision, headache, frontal pyoceles, recurrent orbital abscesses, frontal fistula and secondary frontal-sinus operations explain why rhinologists are loath to risk this type of "complete operation."

Surgery, such as that done with this patient, is successful, so far as the local nasal result is concerned, in 2 out of 3 cases reported[7] in a review of a group numbering 276. Because of the further surgical intervention required in about a third of the patients, with or without asthma (95 of the 276 patients required two to nine frontal operations), convincing evidence of the need for surgery is of the utmost importance before such management is embarked upon.

In summary, my experience is that the nasal cavities can be improved mechanically and physiologically by correction of deviations of the septum and, in patients with vasomotor rhinitis, by subepithelial diathermy coagulation cauterization of the inferior turbinates as described. Further benefit results from removal of nasal polyps, and of polypoid or hypertrophic middle turbinates in large part, as well as of hypertrophied posterior tips of the inferior turbinates. If pansinusitis is present, intranasal antrostomy and ethmosphenoidectomy can be simultaneously performed. Atrophic rhinitis will not supervene unless septal-flap destruction occurs, or unless the inferior turbinates are damaged beyond the limits just mentioned. The nasal operations described above should never be performed on patients who have an atrophic type of nasal mucosa or atrophic rhinitis or nasal tuberculosis.

The Caldwell–Luc antrum operation is a relatively simple and effective measure for dealing with antral disease. This can be done initially if the surgeon so desires. It will not relieve nasal obstruction in most patients with the manifestations of allergy.

External ethmoidectomy, when skillfully done, is a sure method of emptying all ethmoidal cells. Because of the scar on the face, patients are apprehensive of it. The argument that it removes orbital prolongations or other cells not reached by

the intranasal approach does not seem important if a diseased frontal sinus is not also emptied. I have not been impressed by its advantages in vasomotor rhinitis and asthma, and rarely use it in their treatment.

External frontal-sinus surgery should be avoided in the great majority of such patients, because of the probability of local postoperative complications, which occur sooner or later in about a third of the cases and which may make the "cure" seem worse than the original disease.

Finally, in any type of nasal or sinus surgery dealing with polyps and polyposis, the polypoid tissue tends to recur in most patients regardless of the "completeness" of the operation done.

Nasal Polyps and Polypoid Degeneration in Asthma and Vasomotor Rhinitis

The hypothesis that a specific "allergy virus" or "nasal viral infection" may cause nasal and sinus polyposis, asthma and vasomotor rhinitis, is interesting, for it can be utilized to explain many of the facts of intrinsic allergy. If virus protein or virus infection in nasal and sinus polyps and polyposis were the etiologic agent in intrinsic asthma and allied conditions, such a hypothesis would explain most of the vagaries of asthma in relation to nasal and sinus surgery.

A virus lives within an animal or plant cell. If the host cells are not killed by the virus and both the virus and the cells multiply optimally (as possibly in polyposis), the resulting condition may persist indefinitely. Disturbance of such a balance — for example, by surgery — might alter the disease process proportionally.

Humoral antibodies cannot attack an intracellular virus. But cell damage by surgery would permit such an attack because a damaged cell would admit antibody. Any kind of intranasal trauma is occasionally followed by a remission in intrinsic asthma.

Immunity in virus disease is identical in its basic principles with that of other infections. The presence of an optimal quantity of intracellular "viral antigen" in the upper respiratory tract might confer immunity for the period in which the balance was correct. But if the hypothesis stated were correct, alterations in equilibrium would conceivably induce flare-ups in the patient with intrinsic asthma or vasomotor rhinitis, and it is well known that these patients have remissions and exacerbations without apparent reason. The "virus theory" would explain this variability as well as the "cures," possibly by mutation or multiple successor strains of the same virus.

In certain viral maladies only stimulation of cells occurs. If an "allergy virus" or viral allergy induced this type of reaction in the nasal mucosa, it would explain the persistent polypoid degeneration seen in many patients with asthma and vasomotor rhinitis and also the clinical control of such tissue only by excision or by diathermy coagulation destruction.

Clinical observation shows that in asthma and vasomotor rhinitis the virus of the common cold strikes the nasopharynx initially, not the nasal cavities, or both simultaneously, as in normal people. Once the infection is established, however, the allergic patient usually experiences an exacerbation of the asthma or vasomotor rhinitis or both, and nasal polyps not previously visible may suddenly appear. Whether this is due to a virus or to a simple bacterial secondary infection is problematical.

Two patients with extremely severe asthma have had interesting responses to therapy with aureomycin (now on the market as "Duomycin"). Aureomycin is known to affect some respiratory viral infections favorably. After aureomycin therapy one patient's epinephrine intake dropped 90 per cent, from 40 injections daily to 4, and her improvement has continued for several months. The second patient had previously had violent asthma invariably with every cold, however slight, and had been in bed for ten months of the previous year; for five months she had been hospitalized, and she had often required oxygen. In the presence of an acute bilateral maxillary and ethmoid sinusitis, an inflamed tracheal mucosa slowly developed. She was given aureomycin, which seemed to help the nasal infection and to clear the tracheitis completely; no wheezing took place. It is extremely interesting that the middle turbinates, which seemed to be normal during a quiescent stage (as were the sinus x-ray films) developed the appearance of pale, polypoid, degenerative thickening when the acute sinusitis supervened. When the acute infection subsided somewhat, the polypoid thickening persisted. In spite of further attacks of mild and severe acute upper respiratory infection, she has been well for the past three months, apparently from control of nasal and sinus infection by medical methods, including aureomycin from time to time.

The nasopharynx and nasal cavities are favorite virus habitats in many human beings. Furthermore, patients with intrinsic asthma and vasomotor rhinitis often think that they have a "cold the year round" because their symptoms resemble those of the common cold.

The hypothesis that a specific allergy virus or nasal viral infection may be important in the etiology of intrinsic asthma and allied conditions offers an attractive field for research, and I am endeavoring to have a competent virologist investigate the problem.

Discussion

It is apparent from what has been said that nasal and sinus surgery can give highly satisfactory results in the control of asthma and vasomotor rhinitis. So far as nasal polyps and polypoid degeneration are concerned, it has long been recognized

that mucous polyps are extremely common in allergic conditions of the respiratory tract. Kern and Schenck[10] have suggested that true hypersensitiveness to bacteria in the presence of the allergic factor will explain the etiology of polyps, and failure to reckon with these factors is the primary cause of postoperative recurrence. However, it must be emphasized that highly trained and experienced allergists are often unable to control nasal polyps or polypoid degeneration by their own methods in dealing with extrinsic factors, and have even less success when the allergy factor is regarded as intrinsic. Cooke[11] defines and validates bacterial allergy as follows: typical allergic disease unexplained on the basis of contact with protein substances inhaled or ingested or any allergen arising outside the body; predisposing effect of a previous acute infectious disease, such as pneumonia, pertussis or measles; occasional and prompt relief of long-standing allergic manifestations following drainage or removal of an infected focus; and reproduction of an allergic symptom following an injection of an autogenous, sometimes stock, bacterial vaccine. He makes the further statement, "The conclusion as to a bacterial etiology is often indirect."

Because the assumption of a bacterial etiology is admittedly indirect, research regarding the hypothesis that a specific allergy virus or nasal virus infection may cause nasal and sinus polyposis, asthma and vasomotor rhinitis becomes more attractive.

From the practical point of view, certainly the most effective method at the present time for dealing with nasal polyps and polyposis in intrinsic cases is simple excision or coagulation cauterization of polypoid degenerative tissue as it appears.

If a patient with polypoid nasal obstruction has nasal and sinus surgery, only to find after a few weeks, months or even years that the nasal cavities have again filled with the same degenerative tissue, he regards his operation as having been futile. This simple fact has given the laity the impression that one operation always leads to more, that the patient is never cured anyway.

When it is remembered that sinus surgery either in the presence of polypoid degeneration or without it usually fails to control the nasal obstruction resulting from vasomotor rhinitis, despite the wishful thinking of the surgeon, a further cause of failure and the fear of such surgery on the part of the patient is understandable. These difficulties, together with those already enumerated regarding external frontal-sinus surgery, have made a deep impression not only upon the laity but also upon doctors. Nevertheless, the principles and technics outlined above have resulted in a large number of satisfied patients.

Summary and Conclusions

The effect of nasal and sinus surgery on the manifestations of allergy has always been and is still a controversial subject.

The opinions presented rest upon experience with 783 previously reported cases of asthma or vasomotor rhinitis or both; 276 surgical frontal-sinus cases, mentioned in relation to frontal-sinus problems in the total group (only 10 of the 276 patients had asthma); and other groups, mostly unreported, consisting of 272 surgical cases of vasomotor rhinitis (in which 51 patients had asthma) and 255 surgical asthma cases (including the 51 just mentioned) now under intensive study.

The local nasal condition has been found to improve after operation in about 75 per cent of patients with both asthma and vasomotor rhinitis, provided there is an adequate follow-up period.

Nasal or sinus surgery has improved the asthma in about 50 per cent of the cases of intrinsic asthma, reflex asthma and extrinsic infective asthma.

It is impossible at the present time to select in advance the patient with asthma or vasomotor rhinitis who is certain to receive such benefit, although final follow-up results may alter this conclusion.

Surgery directed toward improvement of the nasal cavities, mechanically and physiologically, and toward lessening sinusitis in the antrum, ethmoid and sphenoid sinuses, offers less risk of a poor local result in the nose and sinuses and probably has as good a chance for improvement in vasomotor rhinitis and asthma as more radical external surgery of the frontal, ethmoid and sphenoid sinuses.

The hypothesis that a specific allergy virus or nasal viral infection can cause nasal and sinus polyposis, vasomotor rhinitis and intrinsic asthma is proposed and offers an attractive field for research.

Some of the reasons for the fear of many doctors and patients regarding nasal and sinus surgery are mentioned.

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FATAL AGRANULOCYTOSIS FOLLOWING THERAPY WITH "PRESIDON" (3,3-DIETHYL-2,4-DIOXOTETRAHYDROPYRIDINE), A NEW SEDATIVE HYPNOTIC AGENT*

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AMONG the nonbarbiturate sedative drugs that have recently been introduced has been 3,3-diethyl-2,4-dioxotetrahydropyridine (pyrithyldione), which has been marketed under the trade name of Presidon. The drug was advertised as a sedative hypnotic predictable in its effect, rapid in onset, with negligible side effects, little tendency to habit formation, slight properties of tolerance and completely nontoxic and safe.

A case of fatal agranulocytosis is presented below, since it is believed that Presidon was the etiologic agent responsible for the patient's fatal illness. It indicates that this sedative hypnotic may not be the safe drug it is believed to be. Since most of the indications for sedatives are elective and the conditions for which it is administered benign, it is best to use drugs that have been shown not to be productive of any serious reactions.

CASE REPORT

A 64-year-old woman had a 10-year history of multiple complaints and nervous symptoms that were believed to be on the basis of an anxiety state. She had been treated for her symptoms during this long period by numerous sedative and analgesic agents, consisting of various barbiturates — namely, phenobarbital, Delvinal Sodium, Nembutal, Seconal and Alurate — and the analgesics aspirin and Empirin. For the past few years she had been having bowel complaints, and 2 years previously x-ray films were said to have shown diverticulitis. She stated that she had been failing ever since she had had several teeth extracted in January, 1948. In April she began complaining of a dull, aching sensation in the midabdomen associated with a disagreeable sense of nervous anxiety. Between April and December she lost 16 pounds in weight and felt exhausted most of the time. At times the feeling in the abdomen was described as stabbing. It was not relieved by food and alkalies. When the usual sedatives and analgesics failed to give her relief, she was given Dilaudid, which proved completely effective. She became addicted to the Dilaudid and by November was requiring it every 3 or 4 hours. She also complained of poor appetite and constipation without any associated diarrhea. A severe insomnia developed because of nervousness and because of a dry cough that began during the night. To help relieve the insomnia and perhaps to decrease the amount of Dilaudid utilized, she was given a trial with Presidon. During the period from November 13 through November 17, she received a total dose of Presidon of nine tablets (equal to 1.8 gm). She received the last dose on the night of November 17. This consisted of two tablets (0.4 gm.) of the drug. She was admitted to the hospital on November 18, under the care of a surgeon, to evaluate her symptoms and to rule out cancer.

The past history revealed that an appendectomy had been performed several years previously. The rest of the past and family history was irrelevant.

Physical examination revealed a well developed, underweight, apprehensive woman. Her skin was pale. The heart revealed a soft systolic apical murmur. Abdominal examination was negative except for very slight tenderness on deep pressure just above the umbilicus. The remainder of the physical examination was negative.

Examination of the blood on November 19 showed a red-cell count of 5,180,000, with a hemoglobin of 97 per cent, and a white-cell count of 6000, with 57 per cent neutrophils and 43 per cent lymphocytes; the red blood cells were normal on smear. Urinalysis was negative. The blood sugar and nonprotein nitrogen were normal. The blood sedimentation rate was 3 mm. in 1 hour. Gastric analysis showed free hydrochloric acid. No abnormalities were seen on sigmoidoscopic examination. X-ray study of the chest demonstrated a minimal atelectasis of the left lower lung not noted on a negative chest x-ray examination 2 months previously. X-ray studies were otherwise not remarkable.

The patient was extremely nervous and insisted upon receiving Dilaudid every 4 hours as she was used to doing at home. The basal metabolic rate on November 24 was + 20 to + 25 per cent. The patient continued to be very nervous and on November 25 she was given Lugol's solution, 10 minims three times a day, and 4 mg. (1/16 gr.) of phenobarbital three times a day, in addition to the Dilaudid. No other antithyroid drugs were administered at any time. On the same day she complained of unusual restlessness, and there was a slight rise of temperature, pulse and respiration. On November 27 she complained of sore throat and headache, severe restlessness and malaise, and at times was incoherent. The situation persisted on the 10th hospital day. On the night of the 12th hospital day, the temperature rose to 102.4°F., and she complained of rectal pain. On the following day the temperature rose to 103.4°F. Physical examination revealed an acutely ill woman; there was an ulceration in the left tonsillar fossa, and the gums were friable. The rectal area was found to be reddened and firm, with the appearance of a severe cellulitis. Urinalysis was negative. Examination of the blood on that day showed a red-cell count of 4,560,000, with a hemoglobin of 88 per cent and a white-cell count of 1600, with 0 neutrophils and 100 per cent lymphocytes. The red cells and platelets were normal on smear.

The diagnosis of agranulocytosis having been established, the patient was given vigorous treatment during the next 6 days. She received 100,000 units of penicillin every 4 hours. In addition, she received during this period streptomycin, 1 gm. per day, two blood transfusions, crude liver extract (3 cc. intramuscularly daily) and daily administration of Pentnucleotide, pyridoxine hydrochloride, berocca-c and parenteral infusions. However, her course was steadily downhill. The temperature varied from 101 to 105.6°F. The pulse was over 100, and the respirations became very rapid, going to 30 and to as high as 60 per minute. On December 3 the white-cell count was 1150, with 100 per cent lymphocytes, and the red-cell count 4,030,000, with a hemoglobin of 88 per cent; a blood smear was normal for red blood cells and platelets. The area around the rectum and vagina had become gangrenous, but no pus was apparent. Culture from the perineal region showed *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*). Blood culture was negative. Bone-marrow examination revealed the complete absence of developing and mature polymorphonuclear leukocytes. There was some generalized hypoplasia, with a decrease in nucleated red blood cells. Megakaryocytes were present in normal numbers. On December 4 a smear showed 1 per cent myelocytes, 12 per cent monocytes and 87 per cent lymphocytes. On December 5 the patient appeared worse and lapsed into coma. Her pulse was weak, thready and rapid. She was digitalized with Cedilanid, and the other leukopoietic and antibiotic

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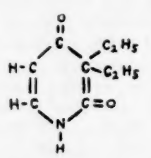
drugs were continued. A blood culture revealed the presence of *Ps. aeruginosa*. On December 6 the white-cell count was reported at 3400, with 3 per cent stab cells, 4 per cent monocytes and 93 per cent lymphocytes. She remained comatose and died that evening (the 18th hospital day) 19 days after the last dose of Presidon and 12 days after the onset of symptoms.

Autopsy revealed the bone marrow to be slightly more cellular than normal, but with an almost complete absence of cells of the granulocyte series, especially of the more mature forms. There was a necrotizing and phlegmonous proctitis and vulvitis with extension into the perineum and adjacent tissues, and edema and probable phlebothrombosis of the lower extremity. Also, there was acute toxic hyperplasia of the spleen and cloudy swelling and toxic degeneration of the liver and kidney. The other findings included slight cardiac dilatation, with acute toxic myocardosis, acute visceral congestion, slight hyperplasia of the thyroid gland, tubular degeneration of the adrenal cortex, slight arteriosclerosis of the aorta and marked hypertrophic arthritis involving especially the vertebral bodies and hands. (The head was not examined.)

Discussion

Presidon is a polymorphous compound containing a pyridine nucleus. Its structural formula is as follows:



The pharmacologic properties of the drug were first reported in 1940 by Koppanyi et al.[1], who discussed the actions and toxic effects of 3,3-diethyl-2,4-dioxotetrahydropyridine, which they refer to as "Pyridione." Given intravenously in repeated daily doses for sixteeen to thirty days to 2 dogs and 2 rabbits the drug was capable of causing a slight drop in the red-cell count; the differential white-cell count and the hemoglobin percentages were within the normal range in these animals. The drug was also given by stomach tube to 14 rabbits for twenty-five to eighty-six daily doses of 15 to 400 mg. per kilogram of body weight each. Within the limits of normal variation there was no change in the blood picture except in 3 rabbits treated intravenously with thirty-five daily doses of 100, 150 and 200 mg., in which there was a shift in the differential count, the level of polymorphonuclear leukocytes being lowered respectively from 34 to 11 per cent, from 24 to 12 per cent and from 19 to 9 per cent. The rabbit receiving the highest daily dose of Presidon, 400 mg. per kilogram of body weight, showed no change in the polymorphonuclear index, the initial value being 43 and the final 47 per cent. This preliminary research with Presidon thus showed that even in therapeutic doses it had a potentially depressant effect on the granulocytic system and that this effect was apparently one of hypersensitiveness rather than an actual toxic depression, since it was not related to dosage.

In published clinical trials, Freed[2] reports chronic toxicity studies on the blood in a total of 19 patients (10 needing the medication and 9 others). The average period of treatment was thirty-eight and two-tenths days. The total dosage range was 18.3 to 7.2 gm. Freed found no effect on the blood count before and after treatment and thought the drug to be an excellently tolerated effective agent, with few aftereffects such as drowsiness, and without apparent allergic reactions. Polatin and Horowitz[3] also noted that 10 patients who received Presidon daily for a prolonged time showed no significant changes in the blood picture, except for a possible transient leukopenia in 1 case that was not associated with any fall in percentage of leukocytes.

When injected intra-arterially into rabbits, Presidon could be found only in traces after a few minutes.[1] In both animals and man only about 5.2 to 12.7 per cent of the drug is excreted.[1, 4] There has been no evidence that there is any accumulation of the drug even if it is given in large doses over a period of four weeks. Thus, the main portion of Presidon apparently undergoes decomposition in the body. The process of its metabolic breakdown in the tissues is not known. Therefore, whether Presidon itself or an intermediate metabolic product of Presidon is responsible for this untoward reaction cannot be ascertained.

The possibility that the agranulocytosis is due to another drug has to be excluded. Twelve years elapsed after the initial article by Schultz[5] before it was clearly ascertained that so-called primary agranulocytosis was almost always secondary to drug therapy.[6-8] Until a few years ago, aminopyrine was found to be the drug involved in the majority of cases of pure agranulocytosis — that is, without an associated pancytopenia. In cases in which other drugs were implicated, it was found that they had usually been given in association with aminopyrine. After this discovery and the elimination from the market of compounds containing aminopyrine, the incidence of agranulocytosis declined greatly. During the past decade, the number of cases has again been on the rise, owing to the introduction of various new drugs, which have proved to be myelopoietic depressants. Of these recently introduced drugs, the sulfonamides[9-12] and thiouracil and other derivatives of thiourea[13] have been most widely implicated. The literature on these etiologic factors is extensive.[10] Many other drugs have been involved on occasions. These are well reviewed in the literature.[11, 12, 14] Also, radium and radioactive materials have been involved. The metallic drugs (gold, bismuth and arsenic) and radium and radioactive substances, unlike aminopyrine, the sulfonamides and thiouracil, very often affect the entire hematopoietic system and not the leukopoietic tissue specifically.

The only drugs taken by the patient described above in the few weeks prior to hospital admission were Dilaudid, phenobarbital and Presidon. Dilaudid and the other opiates have never been implicated in agranulocytosis. The barbiturates have been suspected on several occasions,[15-17] but rarely has there been clearcut proof of their relation to the disease. In most cases the involved barbiturate was taken in the form of a compound that contained also aminopyrine. Hardwick and Randall,[18] in 59 cases, and Teel and Reid,[19] in 3592 cases, found no granulocytopenic effect from pentobarbital. The Council on Pharmacy and Chemistry of the American Medical Association[20] concurred in this observation. Other attempts to produce leukopenia with barbiturates in patients who had recovered from agranulocytosis due to other medication were unsuccessful.[8, 21] Considering the enormous quantities of barbiturates dispensed annually, it is of significance that with one exception,[17] there are no conclusive studies to indicate that the barbiturates are involved. In *New and Nonofficial Remedies* granulocytopenia is not considered among the potential toxic effects of barbiturates. In summary, then, most authors[8, 10-12, 20, 22] believe that the barbiturates apparently do not cause agranulocytosis, and we are impelled to conclude that they were blameless in the case reported above. In the several months prior to the fatal illness, no other medication but Dilaudid and some barbiturates were taken by the patient, and there was no evidence of any specific infection or of exposure to toxic chemicals. In the two weeks before admission only Dilaudid and Presidon were administered. Since Dilaudid and the barbiturates are clearly ruled out, Presidon remains as the almost certain cause of the agranulocytosis.

The time relation for the development of the agranulocytosis is also correct, for Doan[23] has shown that two weeks may be required for the maturation of the myeloblast to the mature five-lobed polymorphonuclear neutrophilic leukocyte. Dameshek and Colmes[24] found the time for the most marked drop of granulocytes after administration of aminopyrine to vary between twelve hours and two weeks. Plum[25] also found the lowest granulocyte counts after the last dose of aminopyrine to vary from one to eighteen days. A similar variation in the onset of clinical symptoms after an offending drug is noted in the literature on the subject. It is possible that the superimposed infection aggravated the toxic depression of the bone marrow in the case reported above. It is interesting to note the monocytic response in the last two days. This has been heralded as a good prognostic sign.[26, 27] Had the patient been able to survive the overwhelming septicemia and toxicity, she might very well have recovered.

The failure to respond to treatment also warrants discussion. The mortality rate was formerly given as 70 to 90 per cent,[11, 12, 25] and, before the drug etiology was recognized, there were many recurrences among patients who recovered. With the introduction of various leukopoietic agents the figures were stated to be from 35 to 50 per cent.[28, 29] Death, which was due to septicemia, pneumonia, hemorrhage following necrosis and various other infections, often occurred even after hematologic improvement had set in. It became apparent that the most important factor in recovery was probably the patient's ability to withstand the sepsis secondary to the lack of granulocytes, since, when the drug was withdrawn, spontaneous recovery of granulopoiesis usually occurred. The period that elapses until the bone marrow can again supply granulocytes to the tissues is a critical one. These considerations led Dameshek and Wolfson[30] to suggest the use of sulfonamides in the treatment of agranulocytosis. After their initial report, numerous successes in treatment appeared in the literature. Since the sulfonamides themselves may cause neutropenia, they have been superseded by penicillin and other antibiotics as they have become available.[31-35] Most recent articles have noted the efficacy of the various antibiotics in tiding the patient over during the acute phase of agranulocytosis until the bone marrow has recovered spontaneously. The greater awareness and earlier recognition of this condition, together with antibiotic therapy, have reversed the mortality rate of 80 per cent, so that now approximately 80 per cent of patients recover regardless of the etiologic agent. Most physicians still use the various leukopoietic agents in treating their cases, especially if they are severe. It is doubtful, however, whether any of these — pentose nucleotide, liver extract, yellow bone-marrow extract and so forth — have much effect.

Failures in therapy still occur for several reasons. Poor results are to be expected if the damage to the bone marrow is massive enough for myelopoiesis to be more than transiently impeded or destroyed. The nature of secondary invaders, the age of the patient, previous state of health and ability to combat bacterial invaders when the patient is stripped of his granulocytic defense are all involved. Our patient received antibiotics in the form of penicillin and streptomycin, and also blood transfusions and leukopoietic agents, including pentose nucleotide, pyridoxine and liver extract. The fatal outcome, however, was consistent with the fact that the period of total lack of circulating granulocytes was relatively long, that the patient was an elderly person with poor previous health and poor tissue resistance and that the bacterial invasion was with *Ps. aeruginosa* (*B. pyocyaneus*), an organism known to be resistant to penicillin and very frequently also to streptomycin.[36] Such overwhelming sepsis was responsible for the patient's death

while she was probably on the verge of recovering bone-marrow function, as noted by the monocytosis.

Summary

A case of fatal agranulocytosis occurring after the use of Presidon is presented. The patient had been given a total of 1.8 gm. of the drug in five days. The only other drugs that the patient was exposed to were Dilaudid and various barbiturates. These agents are not considered to be productive of agranulocytosis, and evidence is presented to show why they should not be incriminated as the toxic agents in this case.

The reasons for lack of recovery even with the use of antibiotics and other adjuvant therapy are discussed.

The observation is made that the number of cases of agranulocytosis has increased in recent years with the introduction of a large number of new therapeutic agents. Many of these drugs were in extensive clinical use before their toxic effects were recognized. A warning is therefore issued that all new preparations should be carefully surveyed for a long period to rule out hematopoietic effects that may prove potentially fatal before the safety of a drug is considered established.

Since sedatives and hypnotics are given as symptomatic and not as specific drugs, agents that may be toxic and can prove fatal should not be used. This is especially true with this class of drugs since the conditions for which they are commonly prescribed are usually benign. The barbiturates when used properly will not produce a fatal reaction. It is believed that the advantages of Presidon over barbiturates are not sufficient to warrant their substitution for the latter drug if our observation of a myelotoxic effect by Presidon is confirmed by other observers.

After this article had been submitted for publication, word was received from the manufacturers of Presidon announcing the recall of supplies of the drug because of reports made to them of leukopenias and agranulocytosis occurring in patients who had been using Presidon. We believe, however, that this case should be recorded in the literature because of the important warnings and conclusions that may be drawn from it.

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QUINIDINE AS A CAUSE OF THROMBOCYTOPENIC PURPURA*

Report of a Case

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BOSTON

IN 1941 Broch[1] reported a case of thrombocytopenic purpura following the administration of quinidine. In 1948 Nudelman, Laff and Howe[2] reported a similar case, which developed after a total dose of 6.0 gm. of quinidine sulfate had been taken. With these two exceptions, the literature appears to be devoid of reports of this type of idiosyncrasy to quinidine. A third case is reported below.

CASE REPORT

On April 14, 1947, a 66-year-old housewife was admitted to the clinic with a complaint of three attacks of spontaneous bruising and bleeding over the previous 7 years. Each attack had been preceded by paroxysmal auricular tachycardia for which quinidine had been prescribed. A very severe but otherwise typical episode had occurred 5 weeks before admission. In accordance with medical advice she had taken 0.37 gm. (6 gr.) of quinidine sulfate when the attack of paroxysmal heart action started, and had taken an additional 0.2 gm. (3 gr.) when it had persisted for 1 hour. Several hours after the first dose of quinidine, abdominal distress, nausea, weakness and a dull headache developed. These symptoms were shortly followed by petechial hemorrhages into the skin of the extremities and trunk and into the mucous membranes of the mouth. There were numerous ecchymotic areas distributed over the body, as well as epistaxis, hematuria and hematemesis. Later in the same day there were four convulsions in rapid succession, and she became comatose. At that time the platelet count was reported as being 85,000, the bleeding time 7 minutes, the clotting time 3 minutes with no clot retraction, the red-cell count 4,000,000, and the white-cell count 10,000. The spleen was said to be slightly enlarged and tender. The patient was treated with snake venom and several small transfusions, and gradually over the course of 3 days the platelet count rose to 400,000, the petechiae cleared, and she recovered.

The past history revealed that the patient had had rheumatic fever at the age of 18. She had been given quinidine sulfate for palpitation on several occasions over the past 15 years without untoward effect until 1940, when the first episode of purpura had occurred. In 1942 purpura again followed the use of quinidine. Quinidine had not been used except on these three occasions since 1940. Each attack had become progressively worse, culminating in the most recent one described above. Vitamin preparations were the only other medication used during this period, and there had been no contact with unusual chemicals.

Physical examination at the time of entry disclosed an obese, elderly woman, 5 feet, 10 inches tall and weighing 254 pounds. The blood pressure was 130/80. There was some stiffness of the neck and knees. The skin was normal except for some stasis dermatitis of the lower legs. There were no purpuric manifestations. Examination of the heart was negative except for a soft systolic murmur at the apex and an occasional extrasystole. The spleen was not felt and did not seem to be enlarged on percussion. There were no abnormal lymph nodes, and the liver appeared to be normal in size. There was a Grade I bilateral pretibial edema. The spleen appeared to be normal in size on roentgenologic examination.

Examination of the blood showed a red-cell count of 5,510,000, with a hemoglobin of 13.2 gm., and a white-cell count of 6350, with 55.5 per cent neutrophils, 2 per cent band forms, 25.5 per cent lymphocytes, 10 per cent monocytes, 2.5 per cent basophils, 4 per cent atypical lymphocytes and 0.5 per cent young lymphocytes. The hematocrit was 41 per cent, and the platelet count 342,000, and the smear was normal. Capillary fragility by the negative-pressure method was slightly increased. The sedimentation rate was 18 mm. per hour, and the blood Hinton test was negative.

Three months after entry the platelet count was again checked and was 380,000. The patient had avoided quinidine and had remained asymptomatic. Five months after entry it was decided to give a test dose of quinidine sulfate to the patient. The result of this experiment is shown in Figure 1.

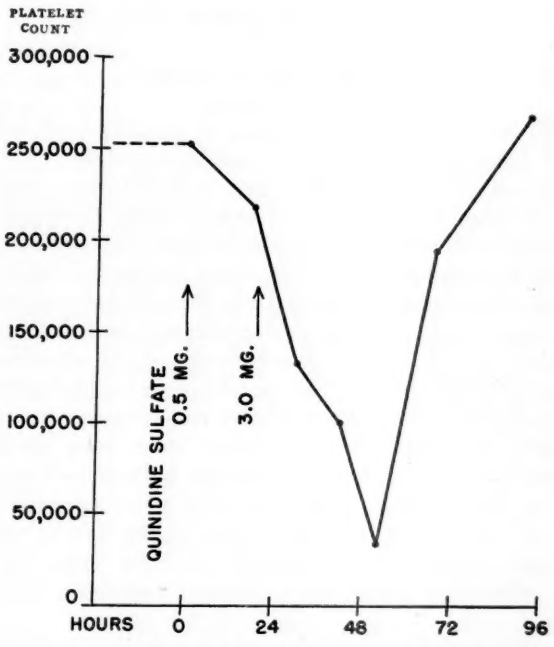

FIGURE 1. *Effect of Test Doses of Quinidine Sulfate on the Platelet Count.*

A very small dose was employed to avoid precipitating a severe reaction. The first dose of 0.5 mg. of quinidine sulfate had no outstanding effect on the platelet count or on the patient, but the second and larger test dose of 3 mg. was followed in 4½ hours by slight abdominal distress, nausea, weakness and a dull headache similar to the early symptoms of her past attacks. Thirty-two hours after the second dose had been given, the platelet count dropped to a low of 33,500. The symptoms mentioned above persisted until the 2nd day after the second dose. At no time did any purpuric manifestations occur, and by the following day the platelets had risen to 194,000. Seventy-two hours after the second test dose the platelet count had reached the pretest figure of 268,000. All platelet counts were done by a modified Dameshek method and were carefully checked, and the stained smears were observed as a further check.

This patient has been repeatedly examined since her entry in April, 1947, and was last seen in November, 1948. The platelet counts have ranged between 234,000 and 330,000. There have been no more purpuric abnormalities.

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Discussion

There can be no doubt that this case represents another example of a rare idiosyncrasy to quinidine resulting in thrombocytopenic purpura. The episode occurring five weeks before entry culminated in cerebral purpura and was almost fatal. It emphasizes the necessity of early recognition of the causative factor in drug sensitivities leading to purpura. In this case the long interval between attacks delayed recognition of the cause and effect relation between quinidine and purpura.

Summary

A case of severe thrombocytopenic purpura following the use of quinidine sulfate is recorded.

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CLINICAL NOTE

ASEPTIC INTESTINAL DECOMPRESSION DURING SURGERY

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THE problem of handling distended loops of bowel has plagued the medical profession for centuries, and it has only been in recent years that a satisfactory solution has been found. With the use of different tubes to decompress the stomach and occasionally the proximal duodenum much upper abdominal distention has been brought under control, and, with the Miller–Abbott and Cantor tubes, in the past ten years control of the intestine has been extended all the way down to the obstructing lesion. The results of the conservative treatment of intestinal obstruction have been most gratifying in restoring physiologic balance in dyspneic, dehydrated, long-obstructed patients before they are subjected to operation, and by having the tube in place postoperatively we have been able to avert the dangerous distention associated with ileus.

The technic of passing the tubes is so widely known that the exact steps are not described here. However, on more than one occasion, the tube has not passed through the pylorus or has advanced so slowly through the gut that satisfactory decompression was never achieved. Since control of chemical balance depends on early relief of trapped gas and secretions, this failure has been extremely disappointing. It is apparent that much must be attributed to luck in the passage of the tip of the tube to its final destination, for in its peregrinations it has many opportunities to get stuck and failure of meticulous co-operation among the doctor, the nursing service and the patient while the tube is en route sometimes delays its passage sufficiently to prolong the issue to an unhappy outcome.

Recently, Cantor-tube decompression was used with fair success preoperatively in 2 cases, and in 2 others the tube was merely introduced into the stomach before operation and then handled by the technic described below. In each case the postoperative course was remarkably benign, with no evidence of ileus, despite the inevitable handling of the gut that accompanies operation for intestinal obstruction.

In 2 cases of obstinate mechanical obstructions the Cantor tube had successfully passed into the small bowel but was making such slow progress toward the critical point that the patient was losing ground. In a thirty-four-year-old pregnant woman obstruction in the fifth month of gestation was due to adhesions from a salpingo-oophorectomy for ectopic pregnancy performed one year before. The second case was a band at the right femoral ring producing a small-bowel obstruction in a sixty-five-year-old woman who had had a cholecystectomy ten days before.

The technic of passing the tube in these 2 cases was very simple once the abdomen was open, despite the fact that the operative field presented a mass of distended, soggy coils of small bowel. The tip of the tube was located, and the loop of bowel just proximal to the mercury-weighted bag was elevated enough to produce an incline. As this was accomplished the tube advanced into a puddle of air and fluid, which was immediately sucked out. By successive lifting of the bowel gently just behind the tip of the tube over 2000 cc. of fluid and a similar amount of air were evacuated within ten minutes, and the tube was passed down to the point of obstruction. The bowel, thus decompressed, presented no problem in exposure, and the corrective surgical steps were made with ease.

As the tube advanced it was able to suck out all the small-bowel contents easily and did not become plugged with chunks of material. We therefore believe that tubes that seem to be plugged during bedside usage may be stopped in an emptied area rather than choked with a plug of material — that is, that they are not advancing satisfactorily rather than performing ineffectually.

In 2 other cases, 1 of adynamic ileus and the other of strangulation of a 10-cm. segment of ileum, the

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Cantor tube was introduced into the stomach, but no delay for its further passage was planned. With the abdomen open the left side of the stomach was lifted anteriorly, and the bag was permitted to slide down through the pylorus. With the anesthetist feeding short lengths of tube to keep up with the advance it was possible to raise each segment of duodenum enough to get the tube to drop throughout the length of the duodenum and around the ligament of Treitz. The free coils of the rest of the small bowel then permitted rapid advance as in the other cases.

To anyone who has experienced the difficulty in advancing simple unweighted tubes through the course of the gastrointestinal tract while the abdomen is open, the simple method described above will be most welcome. One merely takes advantage of gravity to advance the tube, and no traction on the rest of the tube is of any avail, as in our past experience with this and other tubes, which seem to be exasperatingly elusive when enclosed by the bowel. Another interesting finding in the last case mentioned above was that after the bowel had been deflated for about ten minutes the sluggish turgor of its wall disappeared, and stimulations of the wall by pinching provoked healthy waves of peristalsis. Some of the previously distended bowel was incorporated in the anastomosis and handled with ease.

Discussion

Although the best preparation of the small-bowel obstruction for surgery demands a period of observation, hydration and correction of disordered chemical balance early operation with the Cantor tube inserted only as far as the stomach is advocated. We are confident of our ability to move the tube through the difficult spots by the simple use of gravity, and, although such a step was not necessary in our cases, present-day operating tables have sufficient range of mobility to rotate the patient into any desired position. The almost immediate return of bowel tone after deflation permits safe use of the segment for anastomosis, and early complete decompression interrupts the vicious circle of dehydration and fluid loss, which only seems to increase as long as the bowel remains the least bit distended.

Summary

A means of moving a weighted intestinal tube through the bowel is described.

Earlier solution of the acute problem is thus permitted, and complete confidence in the position of the tube upon closing of the abdomen is secured.

Instead of locating the deflated loop distal to the point of obstruction it is suggested that the bowel be deflated down to the obstruction.

Early entry will obviate the occasional case of slow decompression in which the patient is so exhausted by the ordeal that he has insufficient reserve to withstand the operation.

MEDICAL PROGRESS

TOXICOLOGY (Concluded)

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MECHANISMS OF POISONOUS ACTION

Carbon Monoxide

In man, the most simple mechanism of poisoning is that brought about by the inhalation of carbon monoxide. This gas, which is readily absorbed in the lungs, acts by interfering with the ability of the blood to transport oxygen to the tissues. It reversibly poisons the "fluid catalyst," hemoglobin, by forming a compound with it in competition with the compound formed by oxygen. The equilibrium favors the formation of carboxyhemoglobin over oxyhemoglobin by a factor of about 300:1, so that the arterial blood of a person remaining until equilibrium is established in an atmosphere that contains 1 part of carbon monoxide to every 300 parts of oxygen will be half saturated with each gas. A 50 per cent saturation of the blood with carbon monoxide is generally sufficient to cause death. In a sense, this is not due to any peculiar, poisonous properties of carbon monoxide per se, but rather to its limiting of the ability of the blood to transport its full complement of oxygen.

Oxygen therapy is a rational and effective treatment for carbon monoxide poisoning. When the oxygen tension is increased the law of mass action requires that the carbon monoxide tension be increased accordingly. Hence, oxygen aids in displacing carbon monoxide.

The ultimate cause of death in monoxide poisoning is anoxemia resulting in tissue anoxia. Factors in addition to the presence of monoxide frequently aid in the production of the fatal anoxia. At high altitudes, less monoxide is required than at low altitudes. The same conditions prevail in atmospheres in which part of the oxygen has been replaced by nitrogen, or carbon dioxide, or another inert gas. If there is a deficient blood supply to the tissues due to anemia or arterial narrowing, or if through physical exertion there is an increased oxygen demand, death may result from lower carbon monoxide values than would otherwise obtain.

Carbon monoxide poisoning illustrates in a simple manner many of the principles that appear to be involved in other types of poisoning. Unfortunately, few mechanisms of poisonous action approach its simplicity. In many cases a poisonous substance not only inhibits several vital mechanisms simultaneously but also, at the same time, may activate others.

Cyanide

Cyanide is the most rapidly acting poison known. The gas hydrogen cyanide is readily absorbed in the lungs; if present in high concentration it may cause death within a matter of seconds. Alkali cyanides orally ingested act somewhat more slowly, although at the hydrogen ion concentration of the gastric content much of the cyanide present will be in the form of the weakly dissociated hydrocyanic acid. Cyanide does not combine with hemoglobin in the same manner as carbon monoxide does. The blood of the victims of cyanide poisoning is usually fully oxygenated. It does form a compound with methemoglobin, however. Since methemoglobin is not normally present in blood in significant amount it does not greatly influence the action of hydrocyanic acid.

The mechanism of the rapidly toxic action of cyanide is explained by its inhibition of the enzyme cytochrome oxidase.[22] This enzyme acts as a principal intermediary in the oxidation of cytochrome by the oxygen of the blood supply and is an essential functional entity in tissue respiration. Because of this fact, tissue anoxia results as soon as the cyanide reaches the enzyme.

Treatment of nonfatal cyanide poisoning by oxygen is ineffective. Cyanide cannot be so displaced from the cytochrome oxidase. However, methemoglobin, which has a great affinity for cyanide, is capable of competing effectively with the enzyme for the poison. Animals protected by the injection of methemoglobin-forming compounds, such as nitrites, will survive the administration of lethal doses of cyanide.[23] Unfortunately, methemoglobin formers can seldom be administered rapidly enough in human cases to alter the result. Cyanide kills once it reaches a lethal level. If that level has not been attained, the patient will probably survive independently of any treatment, unless the poison is continuing to be absorbed.

Cyanide is believed to be metabolized in man by way of a specific enzyme "rhodanese."[24] This enzyme, which is present in all organs except blood and muscle, is capable of converting cyanide to thiocyanate in the presence of thiosulfate. Thiocyanate is relatively nontoxic and is excreted as such.

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It may be seen, therefore, that the poisonous effect of cyanide is brought about by interference with function of an enzyme essential to respiration; that this action may be prevented by providing methemoglobin, a nonpoisonous competitor for the cyanide; and that the eventual elimination of the poison may be accomplished by a second enzyme, which in turn may be aided in its function by the provision of a suitable sulfur compound as a substrate.

Ethyl Alcohol

With the exception of methyl alcohol, the simple alcohols exhibit very low molecular toxicity. Ethyl alcohol is acutely fatal to man only when it is present in the blood in concentrations of approximately 0.5 per cent. This is more than ten times the normal molar concentration of blood sugar, for example. As for exogenic poisons, very few can reach the blood in such quantities without producing death. It requires over a pound of unmetabolized alcohol in the body to poison an average adult. It is only after the most extraordinary effort that anyone succeeds in accomplishing this result. If the fatal concentration is attained, respiratory depression occurs, followed by terminal heart failure.[25] There is no evidence of irreversible effects of sublethal concentrations of alcohol. Alcohol is absorbed from the entire gastrointestinal tract. It reaches a maximum concentration in the blood between half an hour and two hours after ingestion, and thereafter decreases at a rate proportional to its concentration (about 15 to 20 per cent per hour in man).[26] It is distributed throughout the body according to the water content of the tissues. It is not actively excreted by the kidneys, but diffuses into the ureteral urine in equilibrium with the renal blood supply.[27] About 90 per cent of the ingested alcohol is metabolized; 10 per cent is excreted in urine and breath.[26]

Alcohol is metabolized by way of acetaldehyde to acetic acid.[28] The oxidation occurs principally in the liver, but the brain[29] and other organs to a lesser extent also participate. The first stage of the oxidation is believed to be catalysed by a specific enzyme, alcohol oxidase (or alcohol dehydrogenase).[22] Recently, Keilin and Hartree[30] have shown that catalase, the enzyme that has been thought to be responsible for the destruction of endogenous hydrogen peroxide by catalysing its decomposition to molecular oxygen and water, is also capable of bringing about the coupled oxidation of alcohols to aldehydes. Thus, hydrogen peroxide furnished by the oxidation of glucose oxidase may be employed for the oxidation of ethyl alcohol to acetaldehyde in the presence of catalase. This type of reaction may explain why the oxidation of alcohol is so closely related to carbohydrate metabolism. It has been shown, for example, that the administration of insulin increases the rate of oxidation of alcohol in normal dogs, and is essential to its oxidation in pancreatectomized dogs.[31, 32] Glucose, alanine and pyruvate likewise increase the rate of alcohol metabolism when administered under suitable experimental conditions. Haggard and Greenberg[33] have shown that a high blood sugar level protects rats against fatal alcohol poisoning.

It is interesting to note that there is a normal alcohol content of the human body, which reaches a level of about 0.004 per cent in blood.[34] This may be the equilibrium value necessitated by the presence of minute traces of endogenous acetaldehyde. Under anaerobic conditions (post-mortem anoxemia) alcoholic fermentation occurs, and neoformed alcohol values may reach levels of 0.13 per cent in the blood.[35]

The further oxidation of acetaldehyde to acetic acid is believed to be catalysed by either the enzyme aldehyde oxidase or aldehyde mutase, or both. Under all ordinary conditions, this reaction is exceedingly rapid, so that at no time is an appreciable blood level of acetaldehyde attained. However, there has recently been discovered a class of poisons that inhibits this reaction. The new drug Antabuse is such a substance.[36, 37] The administration of the drug itself does not cause appreciable poisonous reactions, except when alcohol is subsequently administered. The effects are attributed to the accumulation of acetaldehyde brought about by the interruption of the metabolic chain by Antabuse. A poisonous effect has been produced by the simultaneous presence of two substances, each of which is relatively harmless. Ethyl alcohol is made to become toxic by the production of an artificial defect in the enzyme system responsible for its metabolism. It appears likely that similar defects in enzyme systems are of congenital origin[38] and may be responsible for some cases of drug hypersensitivity.

Methanol

Methyl alcohol occupies a unique position in the series of simple alcohols. Its narcotic action is less, and its toxic action much greater than is to be expected from a comparison with other members of the series. If methyl alcohol is ingested, even in small amounts, it gives rise to serious, but delayed, toxic reactions, which in man are characterized by nausea, headache, dyspnea, epigastric pain, cyanosis, impairment of vision and convulsions. The symptoms usually begin as late as eighteen hours after the drinking occurs. Death or permanent blindness results in a high percentage of cases. Death is due to respiratory failure.[39]

Methanol is readily absorbed from the gastrointestinal tract and reaches a uniform distribution throughout the body.[40] In contrast to ethyl alcohol it is eliminated very slowly, being metabolized about one tenth as rapidly.[41] A very high proportion of the methanol is eliminated by breath[42] and urine, although a sufficient quantity is oxidized by way

of formaldehyde to lead to increased elimination of formic acid. In contrast to ethyl alcohol, methyl alcohol may be found in the blood several days after its ingestion.

There has been much research into and considerable speculation about the physiologic basis for the high toxicity of methyl alcohol. Before the common use of pure synthetic methanol the toxicity was believed to be due to impurities and not the alcohol itself. This has been disproved. Most investigators believe that the toxic action (in contrast to the narcotic action) is due not to the alcohol itself but to either of its known metabolites, formaldehyde and formic acid. No completely satisfactory explanation is known at present. However, it is apparent that enzymatic systems related to oxidation-reduction processes are effected.

The same enzyme systems, alcohol oxidase and catalase-dehydrogenase, that are believed to be responsible for ethanol metabolism are available for the oxidation of methyl alcohol. In recent years several investigators have shown that the administration of moderate amounts of ethyl alcohol to men and animals suffering from methyl alcohol poisoning has a pronounced beneficial effect.[43] Ethyl alcohol inhibits the oxidation of methyl alcohol and lessens the excretion of formic acid. Apparently there is competition between the two alcohols for the quantitatively limited enzyme system; ethyl alcohol is preferentially oxidized. Clinically, the poisonous effects of methyl alcohol may be prevented by the continued administration of moderate amounts of ethyl alcohol.[43]

Røe[44] had shown that in human beings (but not in all animals) the toxic effects of methanol are closely related to the degree of acidosis. Impaired vision was frequent in patients with a low alkali reserve, and cyanosis was always present. No patients who died had an alkali reserve that was as great as half the normal value. He believes that the acidosis is not due to the formic acid directly, but rather to its inhibiting effect upon a respiratory process, and to the accompanying accumulation of lactic acid. Treatment of methyl alcohol poisoning, according to Røe, should include the administration of ethyl alcohol to prevent methanol metabolism, and of sodium bicarbonate to counteract acidosis.

Fluoroacetate (Compound 1080)

Sodium fluoroacetate, or compound 1080, is in a sense another product of research activated by World War II. Its unusual toxicity was then first recognized. Yet as a chemical it had been known for many years, and as a poison it had been employed for an indeterminately long period. The West African desert plant "ratsbane" or *Chailletia toxicaria* was long known by the natives to be poisonous to rats, domestic animals and man.[45] It was not until 1944 that Marias discovered that the active principle was potassium fluoroacetate. Independently, during the same year, sodium fluoroacetate was submitted by the Office of Scientific Research and Development to the United States Wildlife Research Laboratory for studies of its possible toxicity. The result was the recognition that herein lay one of the most effective simple poisons known. After intensive tests it has been adopted as a rodenticide and is now employed for the control of rats, gophers and ground squirrels. Its toxicity for dogs and coyotes is high. There have been several deaths among human beings.

Compound 1080 is a white powder, very soluble in water, and readily absorbed through the skin and from the gastrointestinal tract. The lethal dose for most mammals and presumably for man lies between 0.05 and 5.0 mg. per kilogram of body weight. After administration there is a long latent period during which the animal is essentially symptom free. The poison exerts its primary effect upon the central nervous system and the myocardium. Death results from heart failure preceded by arrhythmia and ventricular fibrillation. Epileptiform convulsions are common.[46] Post-mortem findings are nonspecific.

It is difficult to explain the unusual and high toxicity of monofluoroacetate, for as a rule the organic compounds of fluorine are extremely stable chemically, and inert physiologically.[47] For example, neither trifluoroacetate nor the other monohalogen-substituted acetates share the type or degree of toxicity of 1080. Nor is the toxicity due to decomposition and liberation of the fluoride ion. Fluoroacetic acid retains the chemical stability for which organic fluorine compounds are noted.

The toxic action of 1080 has been attributed by Bartlett and Barron[47] to the inhibition of acetate metabolism. The action was shown to be highly specific, for of many oxidation-reduction systems investigated, only acetate and to some extent pyruvate oxidation were affected. However, it was recently indicated that pyruvate metabolism may be the principal site of inhibitory action,[48] and that this inhibition may be prevented by the administration of ethyl alcohol. Hutchins et al.[48] found that ethyl alcohol acted as an antidote to 1080 in animals if administered within half an hour after the poisoning. Whether this action is specific or simply due to the narcotic action of the alcohol is not yet established with certainty.

Phosphoric Acid Esters (Thiophos and Related Insecticides)

After the enactment of the Eighteenth Amendment and during the early years of prohibition, there occurred throughout the United States an epidemic of paralytic and frequently fatal disease associated with the drinking of the alcoholic beverage Jamaica ginger. "Jake paralysis," as it was known, was found to be due to the adulteration of the beverage with

triorthocresyl phosphate, an oily liquid more commonly and properly used as a plasticizer in the manufacture of synthetic resins.[49, 50]

During the same period similar deaths were occurring in Central Europe, but these followed attempts at induced abortion with the traditional abortifacient, oil of apiol. In these cases it was also found that the product had been adulterated with triorthocresyl phosphate.[51] The mechanism of poisonous action was not known at that time. Metacresyl and paracresyl phosphates, closely related to the poisonous orthocresyl compound, did not have similar properties.

It was not until the intensified toxicologic research of World War II that an understanding of the action of triorthocresyl phosphate was realized.[52] During that period four other phosphoric esters were discovered, all of which acted in a similar manner. One was diisopropyl fluorophosphate (D. F. P.), developed by British investigators, and the others hexaethyl tetraphosphate (H.E.T.P.), tetraethyl pyrophosphate (T.E.P.) and diethyl o-nitrophenyl thiophosphate (Thiophos or Parathion) developed by the Germans. All these substances are highly toxic to man and lower animals. They are pronounced inhibitors of the activity of the enzyme cholinesterase.

Cholinesterase has long been recognized as an important factor in the regulation of the mediation of nerve impulses by acetylcholine. It functions by causing the rapid hydrolysis and destruction of the physiologically active acetylcholine. True cholinesterase is found in nerve tissue and erythrocytes, in contrast to a more nonspecific cholinesterase found in serum. Inhibition of cholinesterase actively simulates a cholinergic effect, by preventing the destruction of acetylcholine. Physostigmine is a reversible inhibitor of cholinesterase activity. The toxic phosphoric esters act in a similar manner, except that the cholinesterase inhibition produced by them is not reversible. Brauer[53] has compared the inhibition of serum cholinesterase activity of a number of phosphoric esters and believes that those which inhibit the enzyme activity the most strongly are those with a high free energy. They react with groups on the enzyme to produce alkylation. In the process the enzyme is inhibited, and the enzyme inhibitor is destroyed. Thiophos and related phosphates are unstable in water solution, being hydrolyzed at variable rates to harmless compounds. In the living organism it is probable that they may suffer degradation even more rapidly.

The toxic phosphoric esters would be of scientific and medical significance only, were it not for the fact that they are powerful insecticides of very great economic importance. Already T.E.P. and Thiophos are employed on an extensive scale as agricultural dusts and sprays. Serious illness and even death have resulted among human beings from careless handling or from accident.[54] However, danger of contamination of food with spray residues is minimal, owing to the rapid hydrolysis of the materials.

The symptoms of poisoning by the cholinesterase-inhibiting phosphoric esters are similar to and exemplified by those of physostigmine. They include initially, dizziness, accompanied by contracted pupils and followed after an interval by nausea, diarrhea, abdominal cramps, twitching, coma and convulsions. Death results from respiratory failure. Atropine is used in treatment after the initial symptoms of poisoning have become manifest.

Arsenic

Arsenic compounds, particularly "white arsenic," have been employed as poisons for human beings since the Middle Ages.[55] They enjoyed a considerable reputation among scheming politicians, who were often reported to have employed professional poisoners to shorten the political career of an opponent. They are also used as economic poisons in the form of insecticides, rodenticides and herbicides, in medicine as organic arsenicals and in chemical warfare as vesicants and sternutators. However, it should be noted that arsenic compounds are not employed as fungicides; in fact several species, including *Penicillium brevicaule*, are capable of growing in an arsenic-rich medium, and of metabolizing the arsenic to a methylated arsine.[56]

The most characteristic physiologic property of arsenic compounds is their neurotoxic action. In man this is manifested by polyneuritis not dissimilar to that brought about by vitamin B_1 deficiency. However, the mode of poisonous action remained obscure until at the beginning of World War II the urgency of providing a means of defense against lewisite, an arsenical vesicant, necessitated a concerted attack upon the problem in Britain. A group of biochemists, under the direction of R. A. Peters, showed that arsenic compounds act as inhibitors by combining with thiol (–SH) groups of some enzymes. Pyruvate oxidase, a catalyst to one of the most essential links in the metabolism of carbohydrates, is principally affected. As a result of this preliminary work, a very effective antidote for lewisite and for arsenic compounds in general was devised. BAL, or British anti-lewisite, is 2:3, dimercaptopropanol, a dithio-analogue of glycerin. Its effectiveness in competing with the –SH enzymes for combination with the arsenic atom is dependent upon the fact that it forms a five-membered ring with the latter. Under physiologic conditions this compound is less dissociated than the compound formed by the enzyme and arsenic. Hence it removes arsenic from the enzyme and permits normal enzymatic action.

It is interesting to note, as pointed out by Stocken and Thompson[57] in their recent review of this sub-

ject, that the similarity of the neurotoxic action of arsenic compounds and vitamin B_1 deficiency is due in both cases to the inability of pyruvate oxidase to function — in the first case because of the inhibition of the enzyme itself, and in the second because of lack of the vitamin coenzyme.

BAL combines not only with arsenic compounds but also with many other heavy metals. It is an effective antidote in mercury, gold, cadmium and zinc poisoning.[58] Its affinity for heavy metals is apparently responsible for its inhibition of certain metal-containing enzymes, including catalase, peroxidase and others.[57] Administration of BAL increases the copper excreted in the urine many times. But, in spite of these effects, it is relatively nontoxic to man and other vertebrates.

Summary

The examples chosen above illustrate several mechanisms of poisonous action. They have one factor in common: the action in each case is brought about by the interference of the poison with a vital metabolic mechanism of a catalytic nature. The catalysts involved are in all probability the same enzymes that in some cases have been isolated and studied in vitro and whose actions are known to be inhibited by the poisons in question. Furthermore, many poisonous substances are degraded by enzymes; the metabolic product may have a greater or less toxic action than its precursor. Acetaldehyde, the metabolite, is more toxic than alcohol. Thiocyanate, the metabolite, is less toxic than cyanide. The rate of destruction of the poisonous substance has a pronounced effect upon its action in the living organism, as illustrated in methanol poisoning. But the poison may also be removed from the site of toxic activity by simple chemical or physical means. Arsenic compounds may be caused to combine with BAL, and carbon monoxide may be removed by an increase in the oxygen tension.

The fact that in a few cases satisfactory explanations of poisonous actions are available should not lead to the conclusion that all such mechanisms are simple. Even if it is admitted that enzymes are the keystones to a knowledge of poisonous action, the statement does not in any way simplify the problem, for the multiplicity of enzymatic processes and the delicate balance between them is becoming more and more apparent. Few enzymes have been isolated in pure form; only a score have been crystallized. Even the most complicated systems that have been studied in vitro are no doubt simple in comparison to those of the living organism. Mechanisms that are apparent in the test tube may never occur in the body. What are thought to be inconsequential side reactions in the living organism may be as essential to a balanced metabolism as the governor to the operation of an engine. What is the function of catalase or alcohol oxidase in the human liver? Are they provided to oxidize an occasional highball, or do they play a more fundamental and continuous role in over-all metabolic processes? The answer would have toxicologic significance.

It is apparent that to understand poisonous processes it is necessary to consider smaller and more fundamental units. In human post-mortem toxicology it is customary to employ large quantities of tissue for chemical analysis. It seems likely that the information obtained therefrom could be supplemented by a histochemical localization of the poison. But even more fundamental would be the demonstration of the sites of inhibited enzyme activity. These appear to be the paths of future progress in toxicology.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36021

PRESENTATION OF CASE

A twenty-five-year-old woman entered the hospital because of generalized "bone" pain.

Six months before entry the patient gave birth to her second child, with no apparent ante-partum or post-partum complications. About six weeks later she noted progressive, nonradiating pain in the sacroiliac region on bending over or lifting. Subsequently, pains developed in the shoulders, hips and costochondral junctions. Concurrently she began to experience progressive, persistent anorexia. The x-ray studies of the spine at about this time were said to have shown abnormalities of the bones. She admitted a 20-pound weight loss during the six months before admission. Six weeks before admission, she entered a community hospital, where she remained for three weeks. A "congested mass" was noted in the left breast at that time.

Physical examination revealed a pale woman in no obvious acute discomfort. The breasts presented moderate to marked nodularity, particularly in the upper outer quadrant of the left side. Multiple nodules varying in size from 0.5 cm. to 1.5 cm. could be palpated, but no single lesion could be picked out as distinctively different. None had the clinical characteristics of cancer. Multiple small nodules varying from 0.5 to 1.5 cm. were present in each axilla. There were small 0.5-cm. nodes in the left supraclavicular space, and others of the same size and up to 1.0 cm. were found in the posterior cervical chains on both sides. The nodes in the groin were not remarkable. The liver was palpable 3 to 4 fingerbreadths, and the spleen 1 fingerbreadth below the costal margin. The uterus was retroverted, and the fundus was not palpated.

The temperature was 98.6°F., the pulse 130, and the respirations 28. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood disclosed a red-cell count of 2,480,000, with a hemoglobin of 8 gm., and a white-cell count of 11,400, with 48 per cent neutrophils, 40 per cent lymphocytes, 9 per cent monocytes, 2 per cent basophils and 1 per cent eosinophils. Slight variation in size and shape of the red cells was noted on the stained smear. Urinalysis showed a specific gravity of 1.004 to 1.016 on several specimens. A Sulkowitch test for urinary calcium was consistently positive, running as high as +++. The serum calcium was 11.4 mg., the phosphorus 2.8 mg., and the alkaline phosphatase 7.2 units per 100 cc. The serum protein was 6.7 gm. per 100 cc., with 3.9 gm. of albumin and 2.8 gm. of globulin. The sodium was 140 milliequiv., the chloride 103 milliequiv. and the potassium 3.5 milliequiv. per liter. The blood sugar was 144 mg., and the nonprotein nitrogen 56 mg. per 100 cc. A phenolsulfonephthalein test showed 10 per cent excretion of the dye in fifteen minutes, with 45 per cent excretion in two hours. A blood Hinton test was negative.

The x-ray films revealed a minute area of bone destruction in both scapulas, several of the ribs, and probably in the dorsal and lumbar spine although the films were unsatisfactory. The films of the skull showed a few small areas of rarefaction. The lamina dura of the teeth was preserved. There was an increase in the lung markings, particularly in the lower-lung fields. The heart was not remarkable. Intravenous pyelograms showed the kidneys to be approximately normal in size. No areas of calcification were seen within the kidneys. The concentration of the excreted dye was very low, and the dye incompletely outlined the kidney pelves, which appeared practically normal in size.

The patient was seen by numerous consultants. A blood smear examined by a hematologist showed

several myelocytes, a rare blast form and a fair number of erythroblasts and normoblasts. No plasma cells were seen.

On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. Frederic C. Bartter*: May we see the x-ray films?

Dr. Stanley M. Wyman: The chest shows considerable decrease in its anteroposterior diameter, which I think accounts at least in part for the apparently increased markings in the lower-lung fields, the lung being less aerated in this region. The heart shadow is not remarkable. There are, as described, several small areas of rarefaction in the tips of the scapulas, in several ribs and possibly in the thoracic spine, the lumbar spine and other visualized bones. The skull shows several small, rather indefinite areas of rarefaction, similar to those seen in the other bones. The lamina dura is very well seen and is not remarkable. The intravenous pyelogram is unsatisfactory because of the patient's diminished renal function, but no definite localized disease is seen.

Dr. Bartter: What do you think about the hands, Dr. Wyman?

Dr. Wyman: I think the hands are essentially normal. I do not see any localized disease.

Dr. Bartter: And the parts of the skull that are not involved by the localized lesions you described—would you consider them normal?

Dr. Wyman: I would.

Dr. Bartter: I shall start out by assuming that this patient had a malignant lesion. Differential diagnosis concerns, chiefly, what type of neoplasia she had.

The first one we must take up is carcinoma of the breast. There are several leads in that direction. The first one is the "congested mass" discovered at the other hospital. The nodules in the breast, the nodes in the axilla and the bone lesions are certainly consistent with metastatic lesions from a carcinoma of the breast. However, there are a number of things against carcinoma of the breast. The first is the fact that the operation was not done at the other hospital. Secondly, no single lesion was "distinctively different" on physical examination here. Both axillas were involved, which would be most unusual; involvement of both posterior cervical lymph nodes would again be unusual, although not impossible in carcinoma of the breast. Finally, most important of all, the spleen was enlarged, and it would be unusual to have carcinoma causing enlargement of the spleen unless there was portal obstruction, for which there is no other evidence. On the whole, I think we can reject carcinoma of the breast, and probably any other kind of carcinoma.

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The next lead we have is that of carcinoma of the parathyroid glands, and its rarity need not deter us here. The high serum calcium, the low serum phosphorus and the high serum phosphatase are in favor of that diagnosis. The high urinary calcium is consistent with the hypercalcemia, whatever the cause. The bone lesions, once again, are not inconsistent with those found in metastatic carcinoma. The enlargement of the spleen, however, is strongly against the diagnosis, and the axillary nodes would be unusual sites of metastasis from the parathyroid glands.

Before going on to consider what she died of, we have to dispose of the question of whether she had hyperparathyroidism. Certainly, with these blood chemical findings, the burden of proof rests on anyone who says that she did not. In the last analysis she may have had hyperparathyroidism, but I think it is most unlikely. In the first place is the normality of the bones that are not involved with the discrete lesions—I refer especially to the noninvolved parts of the skull, the hands and the lamina dura about the teeth. This is strong evidence against metabolic bone disease such as osteitis fibrosa, with hyperparathyroidism. Secondly, the elevated serum calcium may be explained without incriminating the parathyroid glands. In a number of diseases characterized by rapid bone destruction hypercalcemia results, and there is enough destruction to account for this patient's hypercalcemia. Thirdly, the serum phosphatase was high (though only slightly high), but there are two plausible reasons for that. She had lesions of the bones causing bone weakness, which in turn would lead to compensatory overactivity of osteoblasts and may have given rise to a high phosphatase, and furthermore she had involvement of the liver, and that may have caused the elevation of the phosphatase. We need not be concerned about the phosphatase. That leaves us with a low serum phosphorus to be explained if we are to dismiss hyperparathyroidism. I cannot explain it. We have seen a number of patients with extensive tumor metastases in the bones who had a low serum phosphorus, and did not have parathyroid disease. I think on the whole that this patient did not have hyperparathyroidism.

Before I go on to the consideration of malignant tumors, I should mention one disease that produces large lymph nodes, a large spleen, bone lesions and an elevated serum calcium, and might produce nodules in the axillas (if these "nodules" that are described are not lymph nodes but lesions in the skin)—and that is sarcoidosis. This patient did not have a high globulin. That is a bit against sarcoid but by no means conclusive. However, the degree of anemia is entirely inconsistent with sarcoid, and I think we can safely reject it.

The malignant lesions that will cause this picture, including enlargement of the spleen, are the diseases of reticuloendothelial or blood-forming elements. Before considering them in detail, I must say that the evidence we have is not sufficient to arrive at a clear-cut differential diagnosis between various types that must be discussed. The types I have considered are myelogenous leukemia in an aleukemic phase, myeloma, Hodgkin's disease, and lymphosarcoma in one of its various forms.

For myelogenous leukemia in an aleukemic phase, we have the report of myelocytes in a smear and occasional blast forms, apparently too immature for the hematologists to decide what parent cell they represented. In this disease the anemia would be a myelophthisic anemia, and the finding of a "fair number" of erythroblasts and normoblasts is consistent with the degree of marrow replacement this patient must have had. However, in myelophthisic anemia, the presence of a few myelocytes is not unusual and need not lead to the conclusion that the patient had leukemia. Also, it is probably somewhat unusual to have lymph nodes involved and nevertheless to have the disease as nearly completely aleukemic as this appears to have been. Finally, the report states that the platelets were normal. With this degree of anemia caused by leukemia, one would rather expect the platelets to be decreased. I think myelogenous leukemia is the least likely of the possibilities.

Myeloma would explain the picture of anemia, bone lesions and involvement of lymph nodes, liver and spleen and would also explain the high serum calcium. It has been shown that a high serum calcium in myeloma may be due to increase of diffusible calcium or increase of calcium bound to albumin, in the absence of an elevated serum globulin. However, there are a number of points against myeloma, the strongest of which is the patient's age. This patient was extremely young to have developed myeloma. In addition, there is the absence of high globulin, and the absence of Bence-Jones protein (which I assume is ruled out by its absence from the protocol). Finally, elevation of the serum phosphatase is most unusual with myeloma involving bone. As I have said, the elevation may have been due to the liver involvement that this patient had. All in all, myeloma is unlikely in this patient.

We go on to Hodgkin's disease. I think the evidence in favor of Hodgkin's disease is quite good. It would explain most of the picture as it is presented. The age of the patient is right. The finding of normal platelets in the presence of severe anemia is consistent with the diagnosis. Somewhat against it is the fact that we have no history of fever at any time. Possibly the fever existed and was not discovered, or not reported, so that this may not be a very strong point against it. An elevation of the neutrophils is the usual finding in the differential count in Hodgkin's disease; this patient had a lymphocytosis. I do not feel too strongly about rejecting Hodgkin's disease.

The most likely possibility of all is one of the malignant lymphomas, a diagnosis that I believe to be consistent with everything the patient had. Perhaps so severe an anemia in a patient who was not subjected to irradiation is somewhat unusual in malignant lymphoma, and that is the one point against it. However, I think it is the most likely possibility.

There are a few loose ends to be mentioned. We have the high fasting blood sugar, which might make one speculate about tumor in the pancreas — certainly, an extremely rare possibility. The elevated nonprotein nitrogen, with some evidence of renal impairment in the findings of slightly depressed phenolsulfonephthalein excretion and poor concentration on intravenous pyelogram, brings up the question whether or not the patient had tumor in the kidneys. Was some of the nonprotein nitrogen due to the high uric acid resulting from lymphoma? The increase in the lung markings suggests involvement of the lungs with tumor. It would be most surprising to find a lymphoma in the liver and in the axillary and cervical nodes without any in the mediastinum. Although Dr. Wyman finds no evidence for it, I wonder if this patient did not have mediastinal and lung parenchymal involvement.

I suppose that the operation was a biopsy on one of the nodes to settle the matter for us.

Dr. Edward F. Bland: Would the pregnancy have anything to do with the picture?

Dr. Bartter: Not that I can see, unless it caused the tumor to grow faster. That might be in favor of carcinoma of the breast, for these tumors grow much more rapidly in pregnancy. I am not familiar with the effect pregnancy has on lymphoma.

Clinical Diagnosis

Metastatic carcinoma, ? primary in breast.

Dr. Bartter's Diagnosis

Malignant lymphoma.

Anatomical Diagnoses

Carcinoma of left breast, with generalized metastases including right breast, pleura, pulmonary lymphatics, liver, spleen and bone marrow.
Myelophthisic anemia.
Hematopoietic spleen.
Jaundice.
Hydrothorax, serosanguineous, bilateral, severe.
Ascites.
Operative wound: bilateral oöphorectomy.

Pathological Discussion

Dr. Ira T. Nathanson: The physical examination recorded here was done by me. They were nodes rather than nodules in the axilla. Dr. Bartter's

differential diagnosis was the one strongly considered at the time the patient was seen. There was no doubt in our minds that she had a malignant lesion because of the manifestation of the entire process.

Examination of the breast was most difficult. She was seen by several of my colleagues who, also, voiced the same opinion. The most suspicious lesion was the one in the upper outer quadrant in the left breast, not noticeably different from many nodules throughout both breasts. The one noted as measuring 1.5 cm. was not characteristic of carcinoma. The posterior cervical nodes were somewhat enlarged and soft. We entertained a primary diagnosis of carcinoma of the breast with extensive metastases and realized that we could not assign a primary focus to any one nodule. However, it is not too uncommon to see the first manifestation of carcinoma of the breast in the form of metastases such as occur in the bone. The primary focus sometimes may be silent for a long time before it manifests itself. I stated that I would not be surprised if biopsy of both axillas and both posterior cervical nodes showed inflammatory changes.

The axillary node was reviewed with Dr. Mallory, and there was a malignant process present; examination of the cervical node was negative. He stated that he could not be sure that the axillary node was characteristic of cancer of the breast, although it was compatible with it. With that in mind, and because this disease was so extensive and consistent with cancer of the breast we bet on that diagnosis. I might say that when the biopsy was done on the breast, too, it was negative in that one area. We removed her ovaries about two weeks after the biopsy. The ovaries, interestingly enough, were practically replaced by tumor, suggesting that this might be of breast origin, since metastases from the breast to the ovaries are quite common. Her response to oöphorectomy was most dramatic. She gained 40 pounds, the bone pain disappeared, she began to make her own blood, and she remained in excellent condition for a year before rapid reactivation in the bones and liver. During this time practically all the nodules also disappeared as judged by physical examination. Of great interest to us at the time of reactivation was the development of obvious carcinomatous foci, in the breast, for the first time, one in the lower inner quadrant and the other in the suspected area in the upper outer quadrant. She had extensive liver disease at the time she came in. The liver finally became enormous as I remember it. When the patient was first seen we tried to explain the enlarged liver and spleen on the basis of a myeloid metaplasia as a result of bone-marrow invasion with tumor.

Dr. Tracy B. Mallory: This patient was followed through to autopsy. At that time it was quite evident that she had a primary tumor of the breast with very extensive metastases to the liver. It was almost entirely replaced by tumor. The spleen, at the time of autopsy, weighed 400 gm., which is definite enlargement at the level where it ought to have been readily palpable. Part of the enlargement was due to extramedullary hematopoiesis but there were also numerous tumor cells present in the spleen, which is rather unusual in breast carcinoma. The bones that were examined, chiefly from the spine, all showed almost complete replacement of marrow with carcinoma. The pleural surfaces were studded with carcinoma and there was extensive involvement of perivascular and peribronchial lymphatics within the lungs.

Dr. Bartter: Is it not very rare for carcinoma to metastasize to the spleen?

Dr. Mallory: Yes, very uncommon, although we do see it once in a while, and recently we had one case with very extensive cancer metastases to the spleen. It is considered so uncommon that I made the gross diagnosis of Hodgkin's disease and found I was completely wrong.

CASE 36022

Presentation of Case

First admission. A sixty-two-year-old woman, a hospital employee, was admitted to the hospital because of dyspnea and cyanosis.

About a year and a half before admission, on routine chest x-ray examination the heart was found to be enlarged to the left. Except for a slight increase of the markings in the lower-lung field, the lungs were clear. It was then learned that she had had mild dyspnea on exertion for nearly six months. An electrocardiogram at that time showed slight right-axis deviation, but was otherwise normal. Physical examination was negative except for obesity and ulcers of the legs. The latter had been recurrent for ten years, apparently on the basis of varicose veins. The laboratory reported a hemoglobin of 15.9 gm. per 100 cc. During the succeeding year, the dyspnea remained about the same. Six months before admission, a dry, hacking cough developed. About six weeks prior to admission, she began to raise white sputum. Over a six-month period the dyspnea slowly increased, and the patient's activities were more and more restricted. Finally, because of a combination of fatigue, shortness of breath, cough and painful leg ulcers, she had to stop work, and five days later entered the hospital. At no time had there been any hemoptysis, foul sputum, palpitation or chest pain.

No history suggesting rheumatic fever was elicited. She had had influenza in 1919 without sequelae.

Physical examination revealed an obese, cyanotic and dyspneic woman, who felt more comfortable lying down than sitting up. The neck veins did not

pulsate. The lungs were resonant, with moist rales heard faintly at both bases. The heart beat sounded muffled through the thick chest wall, but was regular. A soft, Grade I systolic murmur was heard along the lower left sternal border. The aortic second sound equaled the pulmonic. There was no ankle or sacral edema. In the right upper quadrant of the abdomen slight resistance and tenderness were present. From the midleg down, the skin was glossy and purple red. Ulcers over the malleoli were surrounded by tender zones. The dorsalis pedis pulses could not be felt.

The temperature was 98°F., the pulse 104, and the respirations 28. The blood pressure was 150 systolic, 95 diastolic.

Examination of the blood disclosed a red-cell count of 5,500,000, with a hemoglobin of 14 gm., and a white-cell count of 10,600. The urine and stools were normal. X-ray study of the chest showed no change in the heart configuration since the preceding film. The cardiothoracic ratio was 15.7:29.2. On the first x-ray film it had been 14.7:27.2. The lung fields were clear. In the electrocardiogram right-axis deviation was again present. In addition the T waves were low in Lead 1, diphasic in Lead 2 and 3, slightly inverted in CF_2 and CF_4 and flat in CF_5.

The pulmonary vital capacity was 1.8 liters. The venous pressure was equivalent to 110 mm. of water. The arm-to-tongue circulation time with both calcium levulinate and Decholyn was 32 seconds (normal, 11 to 17 seconds), while the arm-to-lung time with 50 per cent ether was 9 seconds (normal, 5 to 9 seconds).

Treatment consisted of rest, sedation, digitalis and local applications for the leg ulcers. Under this regimen, the basal rales disappeared, but cyanosis persisted. In the third week, the arterial blood oxygen saturation was 73 per cent. With oxygen inhalation the saturation rose to 94 per cent. Sputum culture on several occasions grew predominantly *Staphylococcus aureus*. The patient remained afebrile, the cough almost disappeared, and she was discharged after four weeks.

Final admission (six months later). Following discharge the patient's leg ulcers became worse, and the respiratory distress progressed. She was able to walk only short distances at a time on level floors because of a combination of leg pain and dyspnea and finally had to be readmitted, primarily for care of the ulcers.

On physical examination the patient was cyanotic, dyspneic and orthopneic. There was slight edema of the ankles and legs. No rales were audible in the lung fields. The rest of the examination was much as before except that the leg ulcers had increased in number and size.

The red-cell count was 4,500,000, with a hemoglobin of 17.0 gm., and the white-cell count was 7400, with a normal differential count. The urine gave a ++ test for albumin but was otherwise normal. The blood sugar and nonprotein nitrogen also were within normal limits.

In the hospital the patient's condition remained stationary for a week and then began to deteriorate alarmingly without any apparent precipitating cause. The dyspnea increased, and edema of the trunk appeared. She insisted on dangling her legs, whereupon they became tremendously swollen and the ulcers dripped profusely. The neck veins were seen to pulsate during the fourth week. The heart extended to the anterior axillary line. The pulmonic second sound was slightly greater than the aortic. She had been taking digitalis during this time. The failure continued, and the patient died on the twenty-fifth hospital day.

Differential Diagnosis

Dr. Donald S. King*: I see trouble ahead. I always have it at these conferences when the presenting symptoms are "dyspnea and cyanosis."

There are three conditions to be considered: the cardiac, the pulmonary, and that of the extremities. I shall try to combine the three. As for the heart I believe there was definite right-sided failure, with right-axis deviation shown in the electrocardiogram. Dr. Clark, do you think that the electrocardiogram is consistent with chronic cor pulmonale?

Dr. Richard Clark: That together with digitalis effect would well explain the picture, but I cannot be sure that she had had digitalis before admission.

Dr. Louis K. Dahl: I believe she had been on digitalis before that time.

Dr. King: We must, then, take the digitalis effect into account, but this does not, it seems to me, change the diagnosis of right-sided heart failure.

We shall next consider the lungs and think of the two parts of the lungs: the parenchymal tissue and the vascular bed. I have struggled many times in this amphitheater with this problem, and altogether there have been many cases that have illustrated the different changes that may take place in the pulmonary vessels. As for the parenchymal lung tissue I can see no evidence that points to a primary disease. There were no emphysema, no asthma, no fibrosis, no silicosis and no tumor pressing on a large pulmonary vessel. There were no tumor metastases along the lymphatics, and, in short, nothing in the lung outside the blood vessels to account for the right-sided failure. We come then to the problem of the pulmonary vascular bed. The cyanotic picture may occur in several vascular conditions. One may think first of what is apparently a true essential pulmonary hypertension in which Dr. Mallory has not been able in previous cases to find definite anatomical changes in the blood vessels sufficient to account for a marked cor pulmonale.

The next possible condition is obliterative endarteritis, of which we have seen a number of cases.

*Physician, Massachusetts General Hospital.

Usually Ayerza's disease is mentioned in this connection, although this name is not now limited to syphilis of the pulmonary vessels as was once considered necessary. After endarteritis comes the possibility of pulmonary thrombi, and there is often no x-ray evidence of this condition, although extensive thrombi are shown at post-mortem examination. Then come the cases of multiple emboli, and sometimes there are showers of emboli occurring over many months or years. Finally, there are arteriovenous shunts of various kinds, of which we had a case recently.

Before trying to decide which one of these possible vascular conditions to blame for this patient's right-sided heart failure let us see if we can get help from the X-Ray Department. I would like to be certain that the roentgenologists have said that the x-ray films were entirely normal. The first film was taken two years previously when examination was performed because of six months of shortness of breath. The second set of films was taken eighteen months later at the time of her first hospital admission. I do not believe that x-ray films taken on her second hospitalization are available.

Dr. Touffic Kalil: As you say, there is no pulmonary parenchymal cause for the right ventricular enlargement. The heart itself is a little large. I would have difficulty in telling whether it was left or right ventricular hypertrophy. The ordinary criterion on a single posteroanterior view is said to be raising of the apex of the heart, which is not large. Enlargement to the right does not necessarily mean right ventricular enlargement. The right border may be that of the right auricle and enlargement of the left heart, either the left ventricle or a huge left auricle. Only by fluoroscopic examination can one say that she had enlargement in the region of the ventricle.

Dr. King: You would accept it as a right-sided enlargement?

Dr. Kalil: Yes.

Dr. King: Are the lungs clear?

Dr. Kalil: It does not look like a normal chest, and yet I do not know exactly what it represents. There is increase in the lung markings.

Dr. King: There is a fracture, which I do not believe is of great importance, do you?

Dr. Kalil: I would not think so.

Dr. King: This film was taken at the first examination; are the vascular markings normal?

Dr. Kalil: For a patient of this size, I would say that they appear to be within normal limits.

Dr. King: You see nothing that looks like pulmonary infarct or thrombosis?

Dr. Kalil: No, I do not.

Dr. King: All this negative evidence leaves me somewhat in a quandary. If we are going to assume that there were a great many emboli from the vessels in the extremities it seems to me we should have some x-ray evidence of pulmonary infarcts. The patient had had symptoms for two years, but here we are with essentially normal lung fields in the x-ray films. I am inclined to believe that autopsy showed some changes in the lungs themselves in spite of the fact that the films do not show them. The last x-ray film was taken six months before death, so that we have no recent studies to help us. It seems to me that the choice must be between pulmonary arteriosclerosis, which would ordinarily not give any abnormal x-ray shadow, or multiple pulmonary emboli, which in this case have not resulted in x-ray changes. Multiple thrombi are always possible in such cases, but are less likely to be considered when we have the prolonged phlebitis in the legs as a reasonable source of emboli.

Being forced to make a diagnosis in this case I should choose to make one of numerous small pulmonary emboli with small pulmonary infarcts and probably larger pulmonary emboli at the end of the disease. However, I shall not be at all surprised to find thrombi without emboli or even to find primary changes in the vascular wall without thrombi or emboli. Certainly, if it were not for the varicose veins, one would think less of the possibility of emboli and more of primary vascular changes.

Dr. Tracy B. Mallory: Are there any suggestions, or does anyone want to support any of the other alternatives?

A Physician: In that third x-ray film is there anything in the hilus below the aortic knob?

Dr. King: The pulmonary conus is not prominent here. With the cor pulmonale, one would expect to have had a pulmonic second sound that was louder than that described in this case.

Dr. Clark: Is that a prominent pulmonary artery in the third interspace?

Dr. Kalil: No; it is only slightly prominent.

Dr. King: Would you call it abnormal?

DR. KALIL: If I were reading the film, I would mention it as being slightly prominent.

DR. MALLORY: Dr. Dahl, you followed this patient for some time. Will you tell us what you thought about her?

DR. DAHL: When I saw her ten or fourteen days before death, the process seemed to be more clearly primarily pulmonic than cardiac, but I had no very clear conception of the primary process going on in the lungs. The films were not available at the time. It seemed likely that she had a chronic cor pulmonale. We did not know whether or not she had thrombosis. I wondered about a diffuse vascular disease such as lupus erythematosus or periarteritis nodosa, but I had no real evidence on which to base that.

CLINICAL DIAGNOSIS

Chronic cor pulmonale.
Pulmonary thrombosis?

DR. KING'S DIAGNOSES

Multiple small pulmonary emboli.
Cor pulmonale.

ANATOMICAL DIAGNOSES

Pulmonary endarteritis (Ayerza's syndrome).
Cor pulmonale.
Chronic passive congestion, severe, liver, spleen and kidneys.
Subcutaneous edema, massive, trunk and lower extremities.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy a cor pulmonale was found. The heart weighed 400 gm., and the right ventricular wall measured 6 to 7 mm. in thickness as compared with a left ventricle of only 10 mm. There was considerable coronary sclerosis, with calcification, but there was no evidence of fresh or old involvement of the myocardium. The lungs were heavy from congestion and edema, but there was little emphysema, no fibrosis and no infarcts. The pulmonary artery was dilated, and all its major branches showed yellow patches of atheroma. When the lungs were sectioned, it was noted that the small pulmonary arteries projected stiffly upward from the cut surface and that their walls seemed thickened.

Microscopical examination showed that the majority of the small arteries and arterioles were narrowed as the result of intimal proliferation and reduplication of elastic laminae. Some contained fresh and others partially organized thrombi. There were no clots in the larger pulmonary vessels.

We are left with the recurrent problem of trying to decide whether this was primary disease of the pulmonary arteries with secondary thrombosis or whether the entire picture can be explained on the basis of a succession of minute emboli with organization and recanalization. There is no certain way of differentiating histologically. When the vessels involved are as small as they were in this case, the absence of any major emboli or any evidence of infarction points against embolism but is not conclusive. We did classify it as primary pulmonary endarteritis.

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DOGGED DOCTORS

Harper's Magazine, in two facile articles by Milton Mayer, published in the November and December issues of that periodical, demonstrates two possible assumptions. One of these, becoming increasingly evident as one peruses the first article, — "The Rise and Fall of Dr. Fishbein," — is that Mr. Mayer, despite a grudging admiration of the subject of his sketch, does not wholly approve of him. The second, which appears to be almost proved by the time page 13 of "The Dogged Retreat of the Doctors" is reached amounts to a suspicion that Mr. Mayer does not approve of the doctors, either, and can scarcely abide the American Medical Association.

It is unfortunate for the cause of free enterprise and independent action, which the medical profession of this country has espoused, that Mr. Mayer should have turned his — and *Harper's* — face away from the profession, for his style is pungent, his wit scintillating and his array of arguments impressive. Thus, according to Mr. Mayer's philosophy, "If medicine is necessarily a mystery to the average layman, nearly everything else is necessarily a mystery to the average doctor." And again, "The Delegates (of the American Medical Association) meet twice a year to ratify, in practice, the proposals of the Board of Trustees, which, in principle, is responsible to the House."

Mr. Mayer has more ribbons to his typewriter than that of pure reason, however; he is also a master of the insidious propaganda of understatement. Thus, in discussing the birth of Blue Cross in 1932, which at first met with considerable opposition, particularly from the *Journal of the American Medical Association*, he writes:

> The hard-hit hospitals accepted the Blue Cross insurance plan. The A. M. A. wouldn't touch it. Medical ethics required the doctor to serve the sick — and forbade him to solicit patients. Thousands of doctors sat in their offices — and waited; millions of sick persons lay in their homes — and waited.

Another example of this temperateness serves also as a further illustration of the sentiments that the author entertains toward the medical profession: "The doctor's profession obligates him to heal the sick, at any cost, at all costs, or at none, though the heavens fall, the landlord evicts, the shoe store replevins, and the public service corporation shuts off the gas."

Here, according to Mr. Mayer, tossing his verbal firecrackers out through the windows of his incorruptible sanctum, lies the doctor's function — or else. His not to make reply; his not to reason why, and so forth.

Mr. Mayer's articles leave only a little doubt as to Mr. Mayer's position on compulsory health insurance. The evidence seems to be that Mr. Mayer is in favor of it. The difficulty is to extricate Mr. Mayer's convictions from their entangling alliance with his display of verbal pyrotechnics.

ASTHMA AND THE PARANASAL SINUSES

ABOUT a third of the patients in whom asthma develops after the age of forty also have trouble in the nose and sinuses. The relation between the two groups of symptoms and lesions is still a difficult

problem to explain, and these cases are hard to manage. On the one hand is the theory that infection in the sinuses establishes a focus of bacterial growth from which products are dispersed to act as sensitizers, and so to set up a "bacterial allergy" and produce an "infective asthma." Operation does good because it eliminates the infection and stops the dispersal of noxious stimuli. On the other hand is the theory that the lesions develop in the bronchi and in the sinuses at the same time and are produced by the same cause. Operation does good — but the effects are only temporary because the original cause is still effective. There is evidence to support each of these theories, but, since this evidence is not conclusive, the subject remains highly controversial and the treatment of patients who have both asthma and paranasal sinusitis remains difficult.

In this issue of the *Journal* Dr. Weille has reviewed his own extensive experience, which shows that local treatment of the nose — particularly treatment that results in a better airway and does not disturb the normal function of the nasal mucosa — relieves the nasal symptoms in 75 per cent of the cases and the wheezing (asthma) in 50 per cent. These results show once more the close relation between the nose and the bronchi: they suggest a true reflex mechanism, but still they do not prove that idea.

Dr. Weille's suggestion that the lesions in both the nose and the chest may depend upon a viral infection of a chronic sort is interesting, even though there is no evidence so far to support the hypothesis. The sudden onset of asthma could be explained in that way, but whether the persistence of symptoms lasting for years could depend upon a persisting viral infection is hard to say. New head colds are prone to excite asthma in persons who are predisposed, and the "virus cold" leads to, or at least is often followed by, secondary infections, which can persist in sinuses or bronchi, or both; the resulting bacterial allergy is one of the present concepts. The other concept is still vague and uncertain, but the idea that stress and strain — at some times somatic and at others psychic, and at most times both — can be a cause of physiologic changes is at least plausible. Now comes the third and new idea that an acute cold caused by a virus can become a chronic viral infection, and that is quite another matter.

The suggestion is very interesting, and is well worth investigation; its solution will not be easy.

CAVEAT EMPTOR

In a laudable though sometimes overenthusiastic endeavor to synthesize and market new and better drugs for old and distressing illnesses the fact is sometimes lost sight of that, though effective, some of these drugs eventually prove harmful.

It seems definitely proved, for example, that folic acid will bring about a remission in pernicious anemia, but there is ample evidence that in some cases paralysis has followed the administration of the drug, and, to the patient, it is quite unimportant whether the paralysis is caused directly by the drug or whether the tendency to neurologic involvement is simply enhanced. Benadryl, used to combat anaphylactic phenomena, may itself cause urticaria. Penicillin (an antibiotic followed by very few untoward effects) may cause severe stomatitis when used in lozenges. The administration of aminopyrine — once thought to be a harmless analgesic — has been followed by death from agranulocytosis in many cases, its toxicity not having been demonstrated until nearly fifteen years after its introduction. The nitrogen mustards have unquestionably caused thrombocytopenia, leukopenia and anemia. The hemolytic staphylococcus has become penicillin-fast.

And now, in this issue of the *Journal*, comes a warning from one author that the very valuable drug quinidine may bring on thrombocytopenia of considerable severity and from others that Presidon, once considered harmless, may cause fatal agranulocytosis. The manufacturers immediately withdrew the product from the market, but it may still be on the dispensing doctors' shelves or in their bags.

The lesson that should be but seemingly has not been learned is that any new drug, however efficacious it may appear, must be regarded as potentially dangerous until the contrary has been proved, and that this may take years; for more often than not the untoward symptoms are due to an individual idiosyncrasy of the patient to the drug rather than to a toxicity of the drug to all persons.

ARMY AND NAVY FOREVER

THE *Bulletin of the United States Army Medical Department* and the *United States Naval Medical Bulletin*, the Secretary of Defense announces, have consolidated as of January, 1950, into a *United States Armed Forces Medical Journal* and its supplement, the *Medical Technicians Bulletin of the United States Armed Forces*. The Air Force has had no bulletin but will share in the new one, with representation on the editorial staff.

The new publication is welcome into the broad field of medical journalism. Apparently the doctors in the armed forces are either more tractable or better able to co-ordinate their activities than are those who direct the actual battles on land or sea or in the air.

Our schools of medicine will graduate annually, from twelve to fifteen hundred practitioners — which, in connection with the increasing emigration of persons who announce themselves medical men, on their arrival, having ascertained the national weakness to patronize strangers, furnishes good grounds for fearing an overstock of physicians.

Boston M. & S. J., *January 9, 1850*

MASSACHUSETTS MEDICAL SOCIETY

AMERICAN MEDICAL ASSOCIATION MEMBERSHIP DUES

The following letter from the secretary and general manager of the American Medical Association will be of interest to all fellows of the Society.

H. QUIMBY GALLUPE, M.D., *Secretary*

To the Secretaries of the Constituent State and Territorial Medical Associations: The House of Delegates of the American Medical Association at its meeting in Washington, D. C., December 6 to 8, 1949, adopted amendments to the By-Laws of the American Medical Association whereby Division One, Chapter II, Tenure of Membership, has been changed to read as follows:

Chapter II. — Tenure and Obligations of Membership; Dues

Section 1. — When the Secretary is officially informed that a member is not in good standing in his component society he shall remove the name of said member from the membership roll. A member shall hold his membership through the constituent association in the jurisdiction of which he practices. Should he remove his practice to another jurisdiction, he shall apply for membership through the constituent association in the jurisdiction to which he has moved his practice. Unless he has transferred his membership within six months after such change of practice, the Secretary shall remove his name from the roster of members.

Sec. 2. — Annual dues, not to exceed $25.00, may be prescribed for the ensuing calendar year in an amount recommended by the Board of Trustees and approved by the House of Delegates. Each active member shall pay said annual dues to his constituent association for transmittal to the Secretary of the American Medical Association.

An active member who is delinquent in the payment of such dues for one year shall forfeit his active membership in the American Medical Association if he fails to pay the delinquent dues within thirty days after notice of his delinquency has been mailed by the Secretary of the American Medical Association to his last known address.

Any former member who has forfeited his membership because of being delinquent in payment of dues may be reinstated on payment of his indebtedness.

You will note that the following important changes have been made:

(A) The word "Dues" has been added to the title of Chapter II.

(B) Chapter II has been divided into two sections.

(C) The first sentence of Chapter II, which read, "Membership in this Association shall continue as long as a physician is a member of a component society of the constituent association through which he holds membership," has been deleted.

(D) The words "of the American Medical Association" have been added after the word "Secretary" where clarification is necessary.

(E) The sentence, "An active member shall pay dues or assessments as may be prescribed by the Constitution or By-Laws," has been deleted.

(F) The words "in the American Medical Association" have been added after the words "shall forfeit his active membership" in the second paragraph of Section 2.

(G) The sentence forming the third paragraph of Section 2, with regard to reinstatement, is a new addition to Chapter II.

(H) A new paragraph, forming the first paragraph of Section 2, providing for annual dues not to exceed $25.00 has been added to Chapter II.

The House of Delegates, on Recommendation of the Board of Trustees, Set the Membership Dues for the Year 1950 at $25.00.

The full effect of the new provisions will have to be studied and developed during the next year. However, the following interpretations of the amended By-Laws are offered for your guidance at this time:

(a) Active membership in the American Medical Association will continue to be limited to those members of constituent associations who (1) hold the degree of Doctor of Medicine or Bachelor of Medicine, and (2) are entitled to exercise the rights of active membership in their constituent associations as provided in Article 3 of the Constitution of the American Medical Association.

(b) A member of the American Medical Association shall lose his membership in the Association when the Secretary of the American Medical Association is officially informed that a member is not in good standing in his component society *or is delinquent in the payment of the American Medical Association dues established by the above change in the By-Laws.*

(c) Forfeiture of membership in the American Medical Association due to failure to pay dues will have no effect on membership in the component or constituent medical societies unless the component or constituent societies amend their respective constitutions and by-laws. It is, therefore, possible that a physician may be a member of his component and constituent societies and at the same time not be a member of the American Medical Association.

(d) The amended By-Laws provide for the collection of the American Medical Association membership dues by the constituent associations for transmittal to the Secretary of the American Medical Association. The detailed method to be adopted by each constituent association will vary in each state. In general, the method utilized by each state for the collection of its own component and constituent association dues should be followed.

Some of the problems involved in the collection and transmittal of dues will be considered in a later communication to you.

It is planned to provide each member of the American Medical Association a membership card and certificate of membership when his dues are paid.

It will be necessary for the Secretary of the American Medical Association to notify those members who are delinquent in the payment of their dues, and this office will, therefore, require a complete list of all active dues paying members.

No changes have been made in the Constitution and By-Laws of the American Medical Association with respect to Fellowship. Eligibility for Fellowship and annual Fellowship dues of $12.00 remain the same. Under the present By-Laws a Fellow will pay for the year 1950 total membership and Fellowship dues of $37.00.

The following members may be exempted from the payment of the $25.00 American Medical Association membership dues: retired members; members who are physically disabled; interns, and those members for whom the payment of such dues would constitute a financial hardship.

No member should be exempted from the payment of his American Medical Association dues who is not exempted from his component and constituent society dues.

GEORGE F. LULL, M.D.
Secretary and General Manager

Chicago, Illinois

DEATH

TITUS — Raymond S. Titus, M.D., of Brookline, died on December 25. He was in his sixty-sixth year.

Dr. Titus received his degree from Harvard Medical School in 1909. He was formerly chief of the Obstetrical Service at the Faulkner Hospital and was a member of the Board of Consultation of the Massachusetts General Hospital and consultant in obstetrics, New England Deaconess Hospital. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, three daughters and seven grandchildren survive.

CORRESPONDENCE

SHATTUCK FAN

To the Editor: It was very pleasant to note in the December 8, 1949, issue of the *Journal* that the Committee on Public Relations of the Massachusetts Medical Society had considered naming an annual citation for Lemuel Shattuck. I cannot think of a more appropriate name to be attached to a citation to laymen for outstanding contributions to medical progress than that of the Boston publisher Lemuel Shattuck. His "Report of the Sanitary Commission of Massachusetts," published in 1850, is a monument in the field of public health and applied vital statistics. Rarely is more eloquent language found in medical literature than Shattuck's appeal for improved public-health measures. The universality of his thinking, as appropriate now as it was a hundred years ago, is shown by the following words from the Report:

> Man accomplishes more in a few months now than formerly in many years. He seems to live faster and longer in the same time. All is energy and progress. If these distinguishing characteristics of the age are wisely directed, by wise men, — if the progress shall be towards good and not towards evil, — it is impossible to tell what future glories are yet reserved for the triumph of the human mind. We are among those who believe that the age of discovery is yet in its infancy; and that, great as are the achievements of the human intellect, others still more wonderful are yet in store for us.

LYTT I. GARDNER, M.D.

Chapel Hill, North Carolina

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Archivum Chirurgicum Neerlandicum. Editor, Collegium Neerlandicum Promovendis Studiis Chirurgicis Constitutum 'a Singulis Societatibus Quarum Cura. 4°, paper, 88 pp. Arnhem, Holland: S. Gouda Quint/D. Brouwer Filiusque, 1949. $8.50 per year.

This new periodical on surgery is the official organ of the Dutch College for the Advancement of Surgical Science, including the various Dutch surgical societies. The publication is printed in English and is issued quarterly. The American agent is the Oxford University Press, New York City.

Lippincott's Quick Reference Book for Medicine and Surgery: A clinical, diagnostic, and therapeutic digest of general medicine, surgery, and the specialties, compiled systemically from modern literature. By George E. Rehberger, M.D. Fourteenth edition. 4°, cloth, 1723 pp., with 302 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $20.00.

This standard reference work has been thoroughly revised, the present revision being the most extensive since the publication of the first edition in 1920. Much obsolete material has been deleted, and the text brought up to date. Differential diagnosis has been emphasized. The book is divided into two parts: general medicine and surgery and all the specialties; and an alphabetic list of drugs with their dosage, solubility, method of administration, physiologic and toxic action, and uses. The second part should prove very valuable as a reference source. The text is concluded with a pharmacologic and therapeutic index. A general index to the first part, consisting of ten long chapters, would be useful for quick reference because of the overlapping of subjects. Dr. Rehberger has been the sole author for thirty years and should be congratulated for his continuous labor on this outstanding book. The text is printed in a two-column format. The publishing is excellent, and the price not excessive, considering the size and large number of pages. The book should prove very useful to the general practitioner and should be in all medical libraries. Librarians will find it very valuable for quick reference.

Hematology: For students and practitioners. By Willis M. Fowler, M.D., professor of internal medicine, State University of Iowa College of Medicine. With a chapter by Elmer L. DeGowin, M.D., associate professor of internal medicine, State University of Iowa College of Medicine. Revised second edition. 8°, cloth, 535 pp., with 184 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. $8.50.

The first edition of this book was published in 1945. The text in the new edition has been thoroughly revised and brought up to date. Material has been added on the use of folic acid in sprue and other diseases and in the treatment of pernicious anemia. The use of urethane in the treatment of leukemia and of nitrogen mustard in the lymphomas is considered. Many changes have been made in the chapters on multiple myeloma, infectious mononucleosis and the hemoglobinurias. The use of radiophosphorus in the treatment of polycythemia and leukemia is discussed. Dr. DeGowin has completely revised the chapter on transfusion of whole blood and blood derivatives, with a detailed consideration of the Rh factor. Lists of references are appended to the various chapters. The publishing is well done.

The Adrenal Gland. By Frank A. Hartman, Ph.D., research professor of physiology, Ohio State University; and Katharine A. Brownell, Ph.D., instructor in physiology, The Ohio State University. 8°, cloth, 581 pp., with 72 illustrations. Philadelphia: Lea and Febiger, 1949. $12.00.

This new work on the adrenal gland is comprehensive in scope, embracing all aspects of the subject from anatomy through the diseases. The material is extensive on physiology, endocrinology and epinephrine. The text is based largely on the published literature. The bibliography appended to the text comprises a hundred and twenty-five pages. There are indexes of authors and subjects. The volume is well published and is recommended for all medical libraries. The price may seem excessive but is probably based on an anticipated relatively small distribution.

Oral and Dental Diagnosis: With suggestions for treatment. By Kurt H. Thoma, D.M.D., F.D.S.R.C.S.Eng., Brackett Professor of Oral Pathology, Dental School, and lecturer on oral surgery, Graduate School of Medicine, University of Pennsylvania. With contributions by Henry Goldman, D.M.D., head, Dental Department Beth Israel Hospital, Boston; and Fred Trevor, D.M.D. Third edition. 8°, cloth, 563 pp., with 776 illustrations. Philadelphia: W. B. Saunders Company, 1949. $9.50.

This third edition of a standard textbook, first published in 1936, has been completely revised with additions to the material on treatment, including the prophylactic treatment with fluorides, subgingival curettage and gingivectomy in periodontal disease and management of intrabony pocket, glossodynia and fractures of the maxillas. Other material has been added on pyramidal fracture, involving the nasal bones and maxillas, fractures of the ascending ramus, coronoid process and the condyloid process, osteosclerosis fragilis generalisata (marble bone disease), erythroblastic anemia (Cooley's anemia), carotid-body tumors and aberrant thyroid tumors. One hundred and ten illustrations have been added. The text is concluded with a long bibliography arranged by chapters. There is a good index. The book is well published and should be in all medical and dental libraries.

Psychosomatic Medicine: The clinical application of psychopathology to general medical problems. By Edward Weiss, M.D., professor of clinical medicine, Temple University School of Medicine, Philadelphia; and O. Spurgeon English, M.D., professor of psychiatry, Temple University School of Medicine, Philadelphia. Second edition. 8°, cloth, 803 pp. Philadelphia: W. B. Saunders Company, 1949. $9.50.

This second edition of a standard treatise has been revised in the light of the knowledge gained during World War II. The chapters have been rearranged so that material of a general character is segregated in the first part, the second being devoted to special applications to general medicine and the specialties. Much of the text has been rewritten, and considerable clinical material has been added. There is a new chapter on psychosomatic diagnosis, including advances in psychologic testing that have been applied in psychomatic diagnosis and prognosis. Likewise, material on social work in relation to psychosomatic medicine and on orthopedic and physical medicine has been added. There is a bibliography arranged by chapters and appended to the text. There is a comprehensive index. The book is well published. It should be in all medical libraries and available to all physicians interested in the subject.

The Technique of Pulmonary Resection. By Richard H. Overholt, M.D., clinical professor of surgery, Tufts College Medical School, surgical staff member, New England Deaconess Hospital, Faulkner Hospital and Joseph H. Pratt Diagnostic Hospital, Boston, consultant thoracic surgeon to Belmont, Bristol, Barnstable, Cambridge, Essex and Norfolk sanatoriums; and Lazaro Langer, M.D., instructor in surgery, University of Cordoba, Service of Professor Juan Martin Allende, Cordoba, Argentina. 8°, cloth, 193 pp., with 71 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $8.00.

This special monograph, which is devoted primarily to the technic as practiced by the authors, includes their original ideas of using the prone position for the patient and the atraumatic and precise dissection of the intersegmental plane, permitting the removal of a segment without the use of clamps. The first four chapters discuss the preoperative preparation and operative preliminaries, general considerations pertaining to all resections and the intrapulmonary and hilar surgical anatomy. The remaining three chapters are devoted to specific resections, post-resection management and complications and postresection thoracoplasty. The volume is well illustrated, and there are a number of plates in color, accounting for the seemingly high price for such a small book. It should be in all collections on surgery of the lung.

Clinical Allergy. By Louis Tuft, M.D., assistant professor of medicine, Temple University School of Medicine, and chief of clinic of allergy and applied immunology, Temple University Hospital, Philadelphia. Second edition. 8°, cloth, 690 pp., with 54 illustrations. Philadelphia: Lea and Febiger, 1949. $12.00.

The objective of this standard treatise, to provide a work for the general practitioner, the medical student and the beginner in the field of allergy, has been maintained in this second edition. The text has been thoroughly revised and brought up to date, and two chapters on allergy to fungi and allergy to inhalants other than pollens or molds have been added. Other new material consists of a number of topics, including antihistamine therapy, the use of biotherapy and aerosol therapy in asthma, the significance of endocrine allergy, atopy in lower animals and the pathological physiology of migraine. The text is divided into four sections: general principles; etiologic types; clinical manifestations; and allergic dermatoses and allergy in relation to the specialties. An appendix contains material on laboratory methods in anaphylaxis and in allergy, directions and rules for allergic and hay-fever patients and lists of foods and their possible allergens and lists of allergens. The work is a practical guide to the subject and is not burdened with a mass of references. There is a short list of books recommended for further reading. There is a good index, and the publishing is excellent. The book is recommended for all medical libraries and for physicians interested in allergy.

Advances in Surgery. Volume I. William DeW. Andrus, chairman, Editorial Board. 8°, cloth, 554 pp., with 50 illustrations. New York: Interscience Publishers, Incorporated, 1949. $11.00.

In this first volume of a proposed series there are seven articles by specialists on traumatic shock, strictures of the common bile duct, factors influencing the regeneration of nerves, the use of antibiotics in surgery, the immersion foot syndrome, blood vessel anastomosis by means of a nonsuture Vitallium-tube method, experimental studies and applications and tumors of bone. Selected bibliographies are appended to the various chapters. There are indexes of authors and subjects.

The Premature Infant: Medical and nursing care. By Julius H. Hess, M.D., senior attending pediatrician, Michael Reese Hospital, Chicago, and consulting pediatrician, Cook County Hospital; and Evelyn C. Lundeen, R. N., supervisor, Premature Infant Station, Sarah Morris Hospital Station of Michael Reese Hospital, Chicago. Second edition. 8°, cloth, 381 pp., with 101 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $6.00.

In this second edition of a standard work, first published in 1941, the authors have completely revised the text. Material on diseases and infections of the eyes and the skin, the anemias, congenital syphilis and methods of feeding has been added. Recent advances in therapeutics and management have been incorporated in the text. The book is well published and should be in all medical libraries and in the libraries of pediatricians.

Annals of Roentgenology: A series of monographic atlases. Volume XVII. *Roentgen Diagnosis of the Extremities and Spine.* By Albert B. Ferguson, M.D., associate professor of orthopedic and fracture surgery, Boston University School of Medicine, and consulting roentgenologist, Children's

and Memorial hospitals, Boston. Second edition. 4°, cloth, 519 pp., with 631 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. $15.00.

This standard reference work has been further enlarged since the addition of material on the anomalies in the lumbosacral area in the reprinting of the first edition in 1941. The new material is devoted to the interpretation of common neoplasms of bone, especially osteogenic sarcoma, Ewing's sarcoma and multiple myeloma. The book has increased almost a quarter of its original size. There are 71 new illustrations. There is a comprehensive general index and an index of case histories. The atlas is well published and should be in all medical libraries and in the libraries of roentgenologists and orthopedic surgeons.

Zinc Ions in Ear, Nose, and Throat Work. By A. R. Friel, M.D. (Univ. Dub.), F.R.C.S.I. 8°, cloth, 59 pp., with 41 illustrations. Bristol, England: John Wright and Sons, Limited, 1948. $2.00.

In this short monograph Dr. Friel describes his method of zinc ionization and electrolysis in the treatment of chronic otorrhea and other diseases of the nose or throat.

The Clinical Management of Varicose Veins. By David W. Barrow, M.D. With a foreword by Arthur W. Allen, M.D. 8°, cloth, 155 pp., with 58 illustrations and 6 tables. New York: Paul B. Hoeber, Incorporated, 1948. $5.00.

This work offers a good summary of present-day viewpoints on the nature and treatment of varicose disease of the lower extremities. The price seems to be a little high for a book of this scope.

Papers on Psycho-analysis. By Ernest Jones, M.D., F.R.C.P. (Lond.), consulting physician to the London Clinic on Psychoanalysis. Fifth edition. 8°, cloth, 504 pp. Baltimore: Williams and Wilkins Company, 1948. $8.50.

The first edition of these collected papers was published thirty-five years ago, and this fifth edition is practically a new collection because it contains nine recent papers not included in the previous editions and because fourteen papers have been omitted. The present volume contains twenty-seven papers, and the complete set comprises eighty-nine papers. The contributions, all of which originally appeared in scattered periodicals, are brought together for the convenience of interested persons. The text was printed in Great Britain. The publishing is excellent. The set of five volumes should be in all collections on psychoanalysis.

Office Management for Health Workers. By Frances King and Louis L. Feldman. 8°, cloth, 164 pp., with 12 illustrations. New York: Commonwealth Fund, 1949. $2.25.

This small book describes the various aspects of the management of a health office. The location, equipment, staffing and committee and board procedures are discussed. Various office systems are considered on the basis of their suitability for various sizes and types of offices. Considerable space is devoted to card and correspondence files and records. A list of reference books concludes the text. There is a good index and the book is well published. It should become the standard manual on the subject.

Geriatic Medicine: The care of the aging and the aged. Edited by Edward J. Stieglitz, M.S., M.D., attending internist, Suburban Hospital, Bethesda, Maryland, and Doctor's Hospital, Washington, D. C., attending internist (geriatrics), Chestnut Lodge, Rockeville, Maryland, consulting internist, Washington Home for Incurables, associate, Washington School of Psychiatry, and special lecturer, Institute of Industrial Medicine, New York University, Bellevue Postgraduate Medical School, New York City. Second edition. 8°, cloth, 773 pp., with 180 illustrations. Philadelphia: W. B. Saunders Company, 1949. $12.00.

This standard composite treatise, written by forty-seven specialists, has been extensively revised, and the text brought up to date since the publication of the first edition in 1943. Considerable material has been added, particularly in connection with the care and guidance of so-called normal aging and aged patients. It is recognized that geriatric medicine is not a specialty in the true sense but that it cuts across many fields of medicine. Material not pertinent to the subject has been deleted. Short lists of references are appended to the various subjects. There is a good index, and the book is well published. It is recommended for all medical libraries and should prove valuable to all general practitioners and specialists.

Trends in Medical Education: The New York Academy of Medicine Institute on Medical Education, 1947. Edited by Mahlon Ashford, M.D. 8°, cloth, 320 pp. New York: Commonwealth Fund, 1949. $3.00.

This volume brings together all the papers, by various authors, read at the Institute on Medical Education, held in New York City, in 1947. The material is divided into six parts: premedical and the selection of medical students; undergraduate; interns and residents; graduate and postgraduate training for specialization; the responsibility of medical schools and hospitals in the education of the general practitioner; and the relation of group practice and community medical services to medical education. The book is well published, except that it lacks an index. It should be in all medical, public and college libraries.

Medicine of the Year: First issue 1949. Editorial direction: John B. Youmans, M.D., dean, College of Medicine, University of Illinois. 4°, cloth, 143 pp. Philadelphia: J. B. Lippincott Company, 1949. $5.00.

This book summarizes the recent advances in the various fields of medicine and surgery. Twenty-one specialists have written on their various subjects. Lists of selected references are appended to the various chapters. The publishing is excellent.

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey, F.R.C.S. (Eng.), F.I.C.S., F.R.S.E., surgeon, and surgeon-in-charge of the genitourinary department, Royal Northern Hospital, London, senior surgeon, St. Vincent's Clinic and the Italian Hospital, surgeon, Consolation Hospital, Lambeth, general surgeon, Metropolitan Ear, Nose, and Throat Hospital, London, and consulting surgeon, County Hospital, Chatham, Potter's Bar Hospital, and Clacton Hospital. Eleventh edition. 8°, cloth, 426 pp., with 657 illustrations. Baltimore: Williams and Wilkins Company, 1949. $9.00.

This special book has enjoyed a remarkable history. It was first published in 1927, and since then there have been eighteen reprintings and editions in English. It has been translated into German, Turkish, Spanish and Bulgarian. Italian, Dutch and French editions are in preparation. Printings were issued every two years, even during the war years. The text of this eleventh edition was originally issued in four paper-covered parts in Great Britain, and in their publication the author overcame great difficulties in printing, manufacturing and color work. There are a number of colored figures in the text. This volume was bound in the United States from imported sheets. The material is well arranged, and the printing well done. The great popularity of the book speaks well for its soundness.

Diagnostic Tests for Infants and Children: Principles, clinical and laboratory procedures, interpretation. By H. Behrendt, M.D. 8°, cloth, 529 pp., with 45 illustrations and 76 tables. New York: Interscience Publishers, Incorporated, 1949. $7.50.

In this volume the author has attempted to bring together in one place the principles, technics and interpretations of clinical and laboratory tests used in the diseases of infants and children. The contents include digestive function, liver-function tests, general and special metabolic tests, inorganic body constituents, vitamin-nutrition tests, cardiovascular system, immunologic tests, renal-function tests, nervous system, tests of hearing and sight, endocrine-function tests and miscellaneous tests (including various blood tests). There is a special chapter by K. L. Kogan on psychologic tests. Bibliographies are appended to each subject. There is a good index, and the book is well published. It should be in all medical libraries and in the libraries of pediatricians and physicians interested in pediatrics.

Human Helminthology: A manual for physicians, sanitarians and medical zoologists. By Ernest C. Faust, M.A., Ph.D., William Vincent Professor of Tropical Diseases and Hygiene, and head of the Division of Parasitology, Department of Tropical Medicine and Public Health, Tulane University of Louisiana School of Medicine. Third edition. 8°, cloth, 744 pp., with 313 illustrations. Philadelphia: Lea and Febiger, 1949. $10.00.

In this edition a standard reference work has been completely revised and brought up to date. New material has been included, especially on Bancroft's filariasis and schistosomiasis. A chapter has been added on the Hirudinea (leeches). The helminths have been classified according to the *International Code of Zoological Nomenclature.* The illustrations have been revised, and thirty-four added. The bibliography has been substantially increased by the addition of the newer literature and now comprises forty-two pages. There are indexes of authors and subjects. The book is recommended for all medical and scientific libraries and to all persons interested in the subject.

Annual Reprint of the Reports of the Council on Pharmacy and Chemistry of the American Medical Association for 1948, with the Comments that Have Appeared in the Journal. 12°, cloth, 155 pp. Chicago: American Medical Association, 1949.

This small volume contains reports of the Council adopted during 1948. They were previously published in the *Journal of the American Medical Association.* It also contains reports of lesser importance, not published in the *Journal.*

The Compleat Pediatrician: Practical, diagnostic, therapeutic, and preventive pediatrics: for the use of medical students, internes, general practitioners, and pediatricians. By Wilburt C. Davison, M.A., D.Sc., LL.D., M.D., professor of pediatrics, Duke University School of Medicine, and pediatrician, Duke Hospital. Sixth edition. 8°, cloth, 256 pp. Durham, North Carolina: Printed by Seeman Printery for Duke University Press, 1949. $4.75 by check with order, or for $5.00 on credit.

This popular manual has been extensively revised in this sixth edition, and the material brought up to date. It is interesting to note that in this edition the price has been raised for the first time, and at that only $1.00. From the publication of the first edition in 1934 through the fifth edition, the price was held at $3.75. In this condensed book the whole field of practical pediatrics is presented in a volume weighing slightly over a pound.

Neurology. By Roy R. Grinker, M.D., director of The Institute for Psychomatic and Psychiatric Research and Training, and chairman, Department of Neuropsychiatry of the Michael Reese Hospital, Chicago; and Paul C. Bucy, M.D., professor of neurology and neurologic surgery, University of Illinois College of Medicine. Fourth edition. 8°, cloth, 1138 pp., with 393 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $12.50.

This standard treatise was first published in 1934. The text has been thoroughly revised, and many sections completely rewritten. The first four chapters of the previous edition have been deleted, and much of the material has been interwoven into the text. An extensive bibliography of a hundred and nineteen pages is appended to the text. A comprehensive index concludes the book. The arrangement and printing are excellent in every way. The book is recommended for all medical libraries and to all neurologists.

Bensley's Practical Anatomy of the Rabbit: An elementary laboratory text-book in mammalian anatomy. Edited by E. Horne Craigie, Ph.D., professor of comparative anatomy and neurology, University of Toronto. Eighth edition. 8°, cloth, 391 pp., with 124 illustrations. Philadelphia: Blakiston Company, 1948. $4.25.

The objective of this manual is to provide a plan for the orderly study of a typical mammal. This new edition has been revised in the light of the experience gained in the laboratory. Some of the material has been completely rewritten. A section on the fetal circulation has been added. Functional, as well as developmental, aspects have been consistently emphasized. The chapter on general anatomy has been expanded to include some material on microscopical structure. The manual was first published in 1931. The material is well arranged and printed with a good large type. The printing was done in Canada.

Voluntary Parenthood. By John Rock, M.D., and David Loth. 8°, cloth, 308 pp. New York: Random House, 1949. $3.00.

This popular book is written for married persons and is intended to help them in planning their families. It discusses the desirability of parenthood, how it may be achieved and how it may be regulated.

Rapid Microchemical Methods for Blood and CSF Examinations. By F. Rappaport, Ph.D., laboratory director of the Biochemical and Serologic departments of the Beilinson Hospital, Petach Tiqva, and laboratory director of the Bacteriologic and Serologic departments of the Hadassah Municipality Hospital, Tel-Aviv, Israel. With a foreword by F. Silberstein, M.D. 8°, cloth, 404 pp., with 72 illustrations and 32 tables. New York: Grune and Stratton, 1949. $8.75.

The methods described in this book have been tested and found to be satisfactory. Some of them represent original work of the author. Many methods have been adapted to subtropical climates. In 1935 Dr. Rappaport published his *Mikrochemie des Blutes,* and the present volume may be said to be an amplification of his original work. The book should be in all medical libraries and laboratories as a reference work.

Regional Ileitis. By Burrill B. Crohn, M.D., consulting gastroenterologist, Mount Sinai Hospital, New York. 8°, cloth, 229 pp., with 74 illustrations. New York: Grune and Stratton, 1949. $5.50.

This monograph analyzes the literature on the so-called regional ileitis, first named as such in 1932, and on the related forms of ileojejunitis and ileocolitis. The bibliography appended to the text comprises 257 titles. The small book is well published, but the price seems excessive. As a monograph it should be in medical libraries and should prove interesting to gastroenterologists.

Operative Technic in General Surgery. Edited by Warren H. Cole, M.D., professor and head of the Department of Surgery, University of Illinois College of Medicine, and director of surgical service, Illinois Research and Educational Hospitals, Chicago. With an introduction by Frank H. Lahey, M.D. 8°, cloth, 951 pp., with 521 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1949. $16.00.

This first volume of a two-volume treatise is the joint work of thirty-four contributors, all of whom are specialists on the subjects on which they write. The volume covers the field of general surgery. The volume on special surgery will be published later in the current year. Together they will cover the whole field of operative surgery. The material is well organized, and the text well written and edited. Lists of selected references are appended to the various chapters. There is a good index, and the publishing is excellent. This new treatise should be in all medical libraries and available to all surgeons.

Experimental Surgery: Including surgical physiology. By J. Markowitz, M.B.E., M.B. (Tor.), Ph.D., M.S. in Exp. Surg. (Minn.), associate professor of physiology, University of Toronto. Second edition. 8°, cloth, 546 pp., with 330 illustrations. Baltimore: Williams and Wilkins Company, 1949. $7.00.

In this second edition of a standard work, first published in 1937, the material has been revised, and the subject brought up to date. The text has been completely rewritten and reset. Much of the technic described is that in use at the Mayo Foundation and the Johns Hopkins Hospital and in Chicago. Much of it is the author's own, including some not previously published. Bibliographies are appended to the various chapters. The book is well illustrated and well printed with a good type. It should be in all medical libraries and should prove valuable to surgeons and physiologists.

The Fundamentals of Pulmonary Tuberculosis and its Complications: For the student, the teacher, and the practicing physician. Sponsored by the American College of Chest Physicians. Editor, Edward W. Hayes, M.D. 8°, cloth, 480 pp., with 79 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $9.50.

This joint work of twenty-seven contributors covers every aspect of the subject, including primary, secondary and reinfection type tuberculosis, and tuberculosis of the larynx and the genitourinary system. There are also chapters on the relationship of tuberculosis and silicosis, tuberculosis and diabetes, and pregnancy and tuberculosis. The text is concluded with a list of books on pulmonary tuberculosis and other chronic diseases of the lungs. The book is recommended for all medical libraries and to all specialists on tuberculosis.

The First Medical College in Vermont: Castleton 1818-1862. By Frederick C. Waite, M.D. 8°, cloth, 280 pp., with 12 illustrations and frontispiece. Montpelier, Vermont: Vermont Historical Society, 1949.

Dr. Waite writes the history of a medical school of the early nineteenth century, located in a small New England town. A number of appendixes follow the text and include a summation of the annual number of graduates in all New England medical colleges from 1820 to 1861 and catalogues of all graduates and nongraduates. The book should be in all historical collections.

Rehabilitation of the Tuberculous. By H. A. Pattison, M.D. 8°, cloth, 250 pp., with illustrations. Livingston, New York: Livingston Press, 1949. $3.75.

The first edition of this special monograph was published in 1943. This third edition has been revised to include considerable new material. The author has had the opportunity of widening his experience by revisiting two or three rehabilitation projects and to visit for the first time two projects in England. There is a good index. The printing is good and was done by the rehabilitation patients at the Potts Memorial Institute, Incorporated. The technical omissions of the edition on the title page and of the original copyright date on the reverse of the title page are probably due to the inexperience of the printers.

Your Child Makes Sense: A guidebook for parents. By Edith Buxbaum, Ph.D. With a contribution by Florence L. Swanson, M.D., and a foreword by Anna Freud. 8°, cloth, 204 pp. New York: International Universities Press, Incorporated, 1949. $3.25.

This small book, written for parents, is divided into three parts. The first, by Dr. Swanson, discusses the physical development and care of the child, and the mother and child; in this chapter the psychologic relationships are considered. Part two consists of three chapters on the development of mouth activities, muscle control and sex development. Part three discusses the relationship of the child with the family and society and consists of three chapters on the child as a member of the family, school and cultural groups. The material is well arranged and well written. A list of books recommended for related reading concludes the text. The type and printing are good, but the lack of an index detracts from the value of the book, although there is a detailed list of contents.

You and Your Fears. By Peter J. Steincrohn, M.D. With an introduction by C. Charles Burlingame, M.D. 12°, cloth, 224 pp. Garden City, New York: Doubleday and Company, Incorporated, 1949. $2.50.

In this small book for the laity, the author discusses fear and its effects on health. Fright in varying degrees and anxiety are common to all persons at some time, and the author from the point of view of an internist endeavors to give sound advice to those afflicted with these emotions.

Medicine. Vol. II. *Diagnosis, Prevention and Treatment.* By A. E. Clark-Kennedy, M.D., F.R.C.P., fellow of Corpus Christi College, Cambridge, and physician to the London Hospital and dean of the Medical School. 8°, cloth, 894 pp. Baltimore: Williams and Wilkins Company, 1949. $7.00.

This second volume of Dr. Kennedy's treatise on medicine discusses diagnosis, prevention and treatment. The first volume was entitled *The Patient and His Disease* and has been previously reviewed. The text is concluded with a good index. The two volumes are paged consecutively. The printing, done in Great Britain, is of excellent quality in a large type on a light-weight, soft paper. The volume is an excellent example of fine publishing. The treatise should be in all medical libraries and should interest all practicing physicians.

Female Sex Endocrinology: Concise therapy. By Charles H. Birnberg, M.D., associate obstetrician, chief of female sex endocrinology and Endocrine Laboratory, Jewish Hospital of Brooklyn. 12°, cloth, 134 pp., with 30 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $4.00.

This manual provides a concise presentation of its subject and is designed to serve as a quick reference source. The material was originally presented in a series of lectures given in a postgraduate course by the author.

Tonics and Sedatives. Selected from his favorites by Morris Fishbein, M.D., editor of the *Journal of the American Medical Association.* 12°, cloth, 120 pp., with 51 original drawings by Page Cary. Philadelphia: J. B. Lippincott Company, 1949. $2.00.

Dr. Fishbein presents in this small volume his favorite humorous items of medical interest, originally published in the *Journal of the American Medical Association,* beginning with 1914. The items published were selected from clippings sent in by physicians and also those selected by the author from various publications. The book should be in all medical libraries and could well find a place in medical-history collections.

Medical Etymology: The history and derivation of medical terms for students of medicine, dentistry, and nursing. By O. H. Perry Pepper, M.D., professor of medicine, University of Pennsylvania School of Medicine. 8°, cloth, 263 pp. Philadelphia: W. B. Saunders Company, 1949. $5.50.

This special work on medical terminology is intended for students but should prove valuable to all persons interested in the formation of medical terms derived from Latin and Greek. The text is divided into four parts. In the first the author explains the meaning of prefixes, suffixes and roots derived from these languages and used in the formation of medical words, the transliteration of Greek, and eponyms and onomatopoetic words. The last three parts are devoted to vocabularies and comprise two hundred and twenty-three pages of the text. These vocabularies are divided into three sections: preclinical subjects (including the basic medical sciences), clinical subjects and dentistry. Each section is again subdivided into subjects, and the total lists number twenty. This arrangement is cumbersome and not practical. A one-alphabet arrangement would have been easier to use. The difficulty of searching twenty alphabets is obviated to some extent by a comprehensive index to all the terms noted in the text. The definitions of many of the terms include explanatory notes. The text is printed with a good, large type. The book should be a medical best seller, and should be a working tool for the medical secretary and the physician interested in medical literature. It is a "must" book for all general and medical libraries. Each staff member of a medical library should be provided with a copy as an everyday working tool.

Psychosexual Development in Health and Disease. Edited by Paul H. Hoch, M.D., New York State Psychiatric Institute, and Columbia University College of Physicians and Surgeons. 8°, cloth, 283 pp. New York: Grune and Stratton, 1949. $4.50. The Proceedings of the Thirty-Eighth Annual Meeting of the American Psychopathological Association, held in New York City, June, 1948.

This volume of transactions presents the papers read at the annual meeting of the society. Twenty-six persons took part in the meeting by reading papers or discussing the various main topics. The material is divided into five parts: orien-

tation; anthropologic approach; clinical and psychoanalytic approach; an address by Dr. Robert P. Knight on therapeutic attitudes toward psychosexual disorders; and the sociologic approach. The book is well printed, and there is a good index. It should be in all medical libraries and in collections on the psychology of children.

A Dublin School of Medicine and Surgery: An Account of the Schools of Surgery, Royal College of Surgeons, Dublin, 1789–1948. By J. D. H. Widdess, M.A. (Dublin), L.R.C.P. & S.I., librarian and lecturer in biology, R.C.S.I. With a foreword by William Doolin, F.R.C.S.I., hon. librarian, Royal College of Surgeons in Ireland, and editor of the *Irish Journal of Medical Science*. 8°, cloth, 107 pp., with 16 plates. Baltimore: Williams and Wilkins Company, 1949. $5.00.

This special history of a Dublin medical school is well written and should be in all medical-history collections. The publishing is excellent, and the small volume is well illustrated. The printing was done in Great Britain.

Industrial Toxicology. By Alice Hamilton, M.D., and Harriet L. Hardy, M.D., physician to the division of occupational hygiene, Massachusetts Department of Labor and Industries, assistant in medicine, Massachusetts General Hospital, consultant, Los Alamos Scientific Laboratory, University of California, Los Alamos, New Mexico, and instructor, Department of Industrial Hygiene, Harvard School of Public Health, Boston. Second edition. 8°, cloth, 574 pp. New York: Paul B. Hoeber, Incorporated, 1949. $7.50.

This second edition of a standard reference book, first published in 1934, has been rewritten and thoroughly brought up to date. Material has been added, including a chapter on beryllium. The subject of radioactivity has been expanded from thirteen to thirty-eight pages. The bibliography has been expanded threefold and totals thirteen hundred references. The material is well arranged and well written. The printing is well done with a good type, on light nonglare paper. The book should be in all medical libraries and manufacturing plants where poisons are in common use or are evolved during manufacturing processes.

Psychological Medicine: A short introduction to psychiatry. By Desmond Curran, M.B., F.R.C.P., D.P.M., psychiatrist and lecturer in psychologic medicine, St. George's Hospital, and civil consultant in psychologic medicine to the Royal Navy; and the late Eric Guttmann, M.D., M.R.C.P. With a foreword by Sir John J. Conybeare, M.C., D.M. (Oxon.), F.R.C.P., physician to Guy's Hospital, London, and an appendix on *Psychiatry associated with war conditions*. Third edition. 8°, cloth, 252 pp., with 19 illustrations. Baltimore: Williams and Wilkins Company, 1949. $4.00.

This small book on psychiatry has been revised and brought up to date. Additions have been made in the chapters on mental deficiency, schizophrenia and hysteria. The appendix on "Psychiatry Associated with War Conditions" has been retained for the present. The paper, type and printing are good. The printing was done in Great Britain.

The Value of Hormones in General Practice. By W. N. Kemp, M.D., Vancouver, B.C. 4°, paper, 115 pp. Minneapolis, Minnesota: Burgess Publishing Company, 1949. $3.00.

The manual has been prepared for general practitioners in their use of the many pharmaceutical hormonal preparations now available. The text is up to date, and the author hopes to be able to keep it so by issuing frequent revisions.

The Science and Art of Joint Manipulation. Vol. I. *The Extremities.* By James Mennell, M.A.,M.D.,B.C.(Cantab.), consulting physician in physical medicine, St. Thomas's Hospital. Second edition. 8°, cloth, 215 pp., with 299 illustrations. Philadelphia: Blakiston Company, 1949. $7.50.

This special work has been revised by the addition of three new and two alternative technics in the manipulation of the shoulder and cuboid joints. A few minor alterations have been made for the purpose of clarifying the text. New illustrations and new x-ray plates have been included. In the first edition, published in 1939, the author made use of the word tension, and he was criticized because he did not use the word traction. After careful consideration of the matter and to make the author's meaning clear, the word traction is used in the second edition. The printing was done in Great Britain, and the publishing is excellent. The illustrations are well done. The volume should be in all collections on orthopedics.

NOTICES

ANNOUNCEMENTS

Dr. D. Richard Freni announces the opening of his office at 55 Broad Street, Lynn, for the practice of general surgery.

Dr. M. B. Molotchick, of 27 Nahant Street, Lynn, announces the limitation of his practice to cardiology and internal medicine.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The following is the schedule of meetings of the Boston City Hospital for January:

Dr. Robert J. Coffey, professor of surgery, Georgetown University School of Medicine, and director of the Department of Surgery, Georgetown Medical Center, will speak on the subject "Acute and Chronic Pancreatitis" in the Dowling Amphitheater, Boston City Hospital, on Tuesday, January 17, at 7 p.m. Drs. Franz J. Ingelfinger and Claude E. Welch will lead the discussion.

Dr. Wesley W. Spink, professor of medicine, University of Minnesota Medical School, will speak on the subject "Studies Concerning the Diagnosis and Treatment of Brucellosis" in the Dowling Amphitheater, Boston City Hospital, on Wednesday, January 18, at 7 p.m. Drs. Chester S. Keefer and Maxwell Finland will lead the discussion.

Dr. Allen O. Whipple, clinical director of the Memorial Hospital Center for Cancer and Allied Diseases, New York City, will speak on the subject "Radical Surgery in the Treatment of Cancer" in the Dowling Amphitheater, on Tuesday, January 24, at 7 p.m. (Discussers to be announced.)

All interested persons are invited to attend.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at the Mount Auburn Hospital, Cambridge, on Wednesday, January 25.

PROGRAM

11:30 a.m. Business Meeting.

12:00 noon. The Surgery of Mitral Stenosis. Dr. Dwight E. Harken. (The evolution of the surgery of mitral stenosis from its original, disappointing phase to its present practical state will be discussed; lantern slides and colored motion pictures will be used to illustrate the lecture, and representative cases in which this form of surgery has been performed will be presented.)

1:00 p.m. Luncheon.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of the New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, February 14, at 8 p.m. The scientific session will be a symposium on inhalation therapy consisting of the following subjects:

The Physiologic Basis for Inhalation Therapy. Dr. Meyer Saklad, director of anesthesiology, Rhode Island Hospital, Providence, Rhode Island.

Pipeline as an Aid to Oxygen Therapy. Dr. Ralph M. Tovell, director of anesthesiology, Hartford Hospital, Hartford, Connecticut.

Organization of an Inhalation Therapy Department. Dr. Bernard D. Briggs, assistant anesthesiologist, Massachusetts General Hospital.

(*Notices concluded on page xvii*)

NOTICES (*Concluded from page 76*)

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

JANUARY 7–28. Springfield Hospital Conferences. Page 1076, issue of December 29.

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

JANUARY 15–18. American College of Allergists. Page 1076, issue of December 29.

JANUARY 17. South End Medical Club. Page 38, issue of January 5.

JANUARY 17. Boston City Hospital House Officers' Association. Page 76.

JANUARY 18. Greater Boston Medical Society. Page 38, issue of January 5.

JANUARY 18. Boston City Hospital House Officers' Association. Page 76.

JANUARY 18–20. Conference on Cardiovascular Diseases. Page xvii, issue of November 10.

JANUARY 24. Boston City Hospital House Officers' Association. Page 76.

JANUARY 25. Middlesex South District Medical Society. Page 76.

FEBRUARY 6. New England Cardiovascular Society. Page 724, issue of November 3.

FEBRUARY 9. Lobotomy and Its Uses. Dr. Storer P. Humphreys. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 14. New England Society of Anesthesiologists. Page 76.

FEBRUARY 20. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

FEBRUARY 20–23. American Academy of General Practice. Page 252, issue of August 11.

APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX SOUTH

JANUARY 25.

NORFOLK

JANUARY 24.
FEBRUARY 28.
MARCH 28.
MAY 3. Anniversary Dinner.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 19

FRIDAY, JANUARY 20

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, JANUARY 23

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, JANUARY 24

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*7:00 p.m. Boston City Hospital House Officers' Association. Dowling Amphitheater, Boston City Hospital.

WEDNESDAY, JANUARY 25

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.

11:30 a.m. Middlesex South District Medical Society. Mount Auburn Hospital, Cambridge.

*12:00 m. Clinical Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

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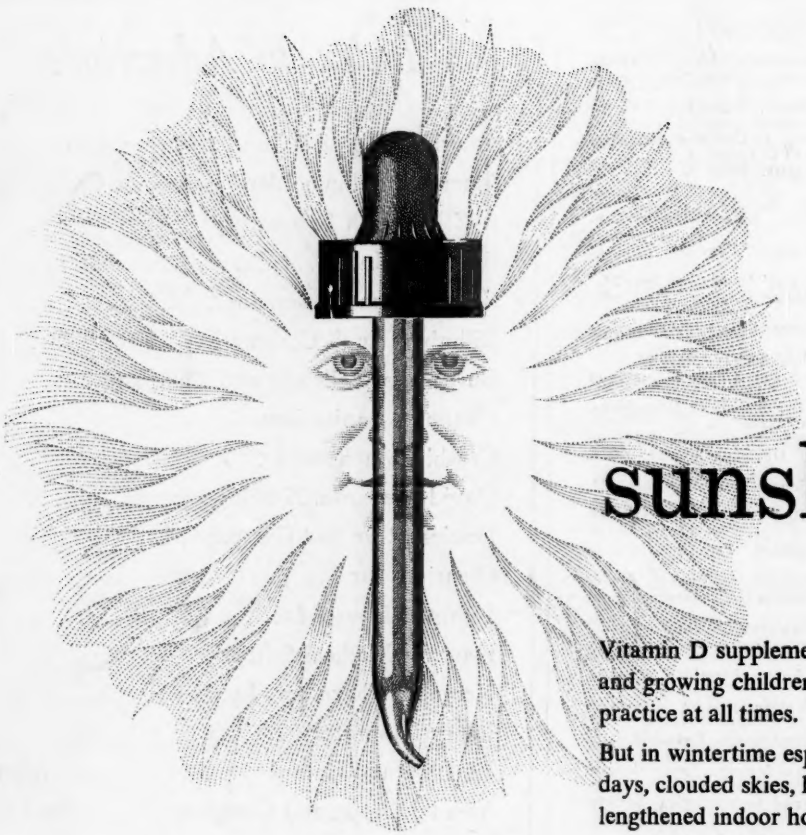

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